CLINICAL DISORDERS
OF THE
PULMONARY CIRCULATION

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Edited by

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FOREWORD

By PAUL WOOD, O.B.E., M.D., F.R.C.P.

This monograph on the pulmonary circulation is a timely and much needed contribution to medical knowledge, for a great deal of work has been done on this subject since the introduction of reliable means of measuring pressure and flow in the pulmonary arteries and veins. That the majority of its authors are on the staff of the Postgraduate Medical School of London or have at one time been connected with that institution is seemly, for it was here that McMichael and Sharpey-Schafer helped to develop the technique that made so many of these observations possible. In their choice of other authors the editors have selected wisely, particularly perhaps in relation to Donald and Lee, whose contributions are outstanding.

For a book of this kind there is remarkably little overlapping or conflict of opinion; only with regard to nomenclature is there any confusion. Being in a privileged position perhaps I may be allowed to comment on this, especially because with the help of J. B. Lowe I was responsible for introducing several of the expressions around which much of the confusion seems to circulate.

Physiologically there are only three fundamentally different kinds of pulmonary hypertension; these may logically be called passive, hyperkinetic and vaso-occlusive. The word passive implies the absence of any active agent on the arterial side that might lead to a raised pulmonary artery pressure, and this denies its use in relation to increased pulmonary blood flow It should be used solely when pulmonary hypertension results only because the pulmonary venous pressure is raised. The term hyperkinetic pulmonary hypertension best describes a high pulmonary artery pressure caused chiefly by increased blood-flow. The adjective was selected because it had long been used to describe a high cardiac output [illegible]

the right ventricle, a situation that does not exist. Hyperkinetic pulmonary hypertension is not passive, because there is an active blood pressure raising agent (increased flow) on the arterial side. The third great group results physiologically from an increased pulmonary vascular resistance, however caused, and this may be called vaso-occlusive pulmonary hypertension. Its chief subdivisions are (vaso) obstructive, e.g. thrombo-embolic, (vaso) obliterative, e.g. from endarteritis fibrosa, and vasoconstrictive (functional), e.g. hypoxic. When an increased pulmonary vascular resistance is secondary to passive or hyperkinetic pulmonary hypertension, the word reactive may be used with advantage when it is desired not to beg the question of mechanism. The term active pulmonary hypertension (once used in cases of mitral stenosis with a high pulmonary vascular resistance to distinguish them from cases of passive pulmonary hypertension) should now be abandoned, for the implication that the reaction is necessarily vasoconstrictive is not justified, and when it is vasoconstrictive that word itself identifies it.

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Subacute cor pulmonale remains the correct label for neoplastic cases with diffuse lymphatic spread, for here the respiratory apparatus is involved, and the physiological disturbance is similar to that associated with diffuse interstitial fibrosis of the lungs. Tumour embolism, from chronionepithelioma, for example, is obstructive pulmonary hypertension and should be so classified. It behaves like primary pulmonary hypertension, not like cor pulmonale.

It should be clear to the reader that these views on nomenclature and classification are my own and their expression in the foreword of this book in no way implies their acceptance by the authors or editors.

No less confusion surrounds the nomenclature and classification of cor pulmonale or the more cumbersome expression pulmonary heart disease. It is abundantly clear, however, that disturbance of the cardiovascular system secondary to parenchymatous disease of the lungs, such as emphysema, requires a definitive title that separates it completely from all forms of pulmonary hypertension in which the respiratory apparatus is essentially normal (as in primary pulmonary hypertension) or only secondarily involved (as in mitral stenosis). To regard primary pulmonary hypertension and the reactive pulmonary hypertension of mitral stenosis, for example, as subdivisions of cor pulmonale is tantamount to identifying cor pulmonale with pulmonary hypertension itself. Nothing is gained and much is lost by so doing. Cor pulmonale, when fully developed, usually means a cyanotic form of heart failure secondary to gross inadequacy of respiratory function. The arterial oxygen saturation is always reduced. When the pulmonary lesion is mainly emphysema, carbon dioxide retention is invariable; when it is mainly interstitial fibrosis, there is no carbon dioxide retention. The pulmonary vascular resistance varies greatly. The frequency of severe pulmonary hypertension in any series depends on what cases are classified as cor pulmonale and what are not. Obviously, if pulmonary hypertension and genuine right ventricular failure are demanded before a diagnosis of cor pulmonale is made, then all such cases of cor pulmonale must have a raised pulmonary vascular resistance. But at the bed-side there are few physicians who would not make the diagnosis when a case of bronchitis and em-

... presented with central cyanosis

the physiological response to the Valsalva test is normal, and digitalis may not help ... In these cases salt and water retention is probably renal and hypervolaemia raises the venous pressure. The absence of right ventricular strain is confirmed by the normal electrocardiogram. That the cardiovascular system is disturbed by the altered blood gases is evident from the bounding peripheral pulse, the relatively high cardiac output, and the diminished renal blood flow. Moreover, each attack of acute bronchitis is accompanied by transient vasoconstrictive pulmonary hypertension. To deny the use of the term cor pulmonale to identify such cases when the pulmonary vascular resistance is normal, but to use it to describe exactly the same disease when complicated by pulmonary hypertension seems illogical and is certainly confusing. I have always pleaded that cor pulmonale should be defined as disturbance of the cardiovascular system secondary to parenchymatous disease of the lungs. ... thoracoplasty or gross obesity, ...

thoracic cage' ...

Of course chronic pulmonary hypertensive cor pulmonale is already subclassified ... form of obliterative pulmonary hypertension.

Such a definition denies the right of massive or multiple pulmonary embolism to be labelled acute cor pulmonale, and the right of recurrent pulmonary embolism to be labelled subacute cor pulmonale. These embolic states represent acute or subacute obstructive pulmonary hypertension, and should be so classified. Acute cor pulmonale might define "heart failure" secondary to bronchopneumonia.

PREFACE

Increasing knowledge and interest in the pulmonary circulation has stimulated us to compile a comprehensive review of the subject and to set out on paper up-to-date views held by experienced workers in this field.

The book is designed primarily for senior students and clinicians who are concerned with the diagnosis and treatment of disorders of the heart and the pulmonary circulation.

The format of individual chapters is not identical, for free expression of views and presentation has been left to every contributor. Some repetition is deliberate to emphasize important or controversial problems.

We are deeply grateful to our contributors for their unstinted efforts and would especially like to thank Professor McMichael for his help and advice with the arrangement of this book.

We should like to thank Messrs E. & S. Livingstone Ltd. and the Editors of *The British Heart Journal, The British Journal of Radiology, Circulation, Clinical Science, The British Medical Journal* and the *Journal of Physiology* and *The Lancet* for permission to reproduce some of the illustrations.

Finally we are most grateful to Dr. Paul Wood, who has written such a stimulating and provocative Foreword The extent to which he is quoted in the text bears witness to his pre-eminence in this field.

R. D.
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R E S

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CONTENTS

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CHAPTER 1

ANATOMY OF THE PULMONARY VASCULATURE

By RAYMOND DALEY

EACH LUNG is divided into ten bronchovascular segments. The pulmonary artery has not quite the same lobar distribution and relative constancy of origin as the bronchi, although there is a fairly constant relationship between the segmental arteries and bronchi. Perisegmental veins travel superficially, immediately beneath the pleura or in intersegmental planes. They course somewhat independently of the segmental bronchi and arteries to reach the subpleural planes in the primary hilum and there join a main pulmonary vein

These differences in the anatomical course of the bronchi and pulmonary arteries and veins make suitable nomenclature difficult. In spite of these discrepancies it has, however, become common practice to name the blood vessels according to the lobes or segments which they serve

The Pulmonary Arteries

The left main pulmonary artery arises in front of the left main bronchus and shortly arches over it to lie, in the hilum, behind and above it and the vein. Here segmental branches are given off to supply the left upper lobe. In the oblique fissure a branch passes to the lingula segment and divides into the superior and inferior segmental arteries There are, of course, variations in the origin of these as of all segmental arteries, but they are of practical importance in the surgical rather than the haemodynamic field.

The four basal segmental arteries usually follow their respective bronchi as the medial and anterior basal segmental arteries, and the lateral and posterior basal segmental arteries.

The right main pulmonary artery arises from the main pulmonary artery and crosses behind the aorta and superior vena cava and in front of the oesophagus In the right hilum the artery lies between the vein and the bronchus It divides into upper and lower branches. The upper supplies the anterior and apical bronchopulmonary segments of the right upper lobe The lower crosses the anterior surface of the right bronchus between the origins of the upper and middle lobe bronchi. This trunk supplies the middle and lower lobes, and, usually, the posterior bronchopulmonary segment of the upper lobe. As in the left lung there are four basal segmental arteries, which are adjacent to their respective bronchi.

The Pulmonary Veins

The left superior pulmonary vein receives all the left upper lobe segmental veins It also usually receives two tributaries from the lingula but these may drain into the inferior pulmonary vein or even directly into the left atrium.

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The left inferior pulmonary vein has five tributaries which run behind their respective bronchi. These number three on the lateral side, the lower lobe apical segmental vein, the anterior basal vein and the lateral basal vein, *and one on the medial side, the medial* basal vein. The termination of the parent vein is called the posterior segmental vein.

The right superior pulmonary vein drains the right upper and middle lobes via three to five trunks. The highest trunk is the apical anterior vein which receives tributaries from the apical and anterior bronchopulmonary segments. Below is the inferior vein which runs subpleurally in the transverse fissure. The two tributaries from the middle lobe usually drain into the superior vein but *may join the inferior vein or even enter the left atrium* directly. The posterior and intersegmental regions of the upper lobe are drained by the posterior segmental vein which enters either the main pulmonary vein or its inferior tributary.

The right inferior pulmonary vein receives the five segmental veins from the lower lobe *which run behind their respective bronchi The highest of these is the lower lobe apical* segmental vein. The lowest is the medial basal segmental vein Between these two are the anterior, lateral and posterior basal segmental veins which have no fixed pattern of entry into the inferior pulmonary vein.

The Bronchial Arteries

The bronchial arteries supply the structure of the lungs including the vasa vasorum *of the pulmonary veins and lymphatic structures in the lungs, hila and at the carina. Many* anatomical studies of their [illegible] recent has been by Cudkowicz an[illegible] techniques after the bronchial a[illegible] They concluded that the bronchial arteries normally arise from the aorta and that, while there is no constancy as to their number or level of origin, the majority lay opposite the fifth and sixth dorsal vertebrae. A common number is two to each lung. As they pass from the aorta to the hilum, either anteriorly or posteriorly to the oesophagus, they send branches to the mediastinum, oesophagus, hilar lymph nodes and the vagi On each side an annulus is formed round the main bronchus and from this the true bronchial and pleural arteries arise.

The true bronchial arteries radiate with the major bronchi, having a branch on either side. These branches frequently communicate in the fibrous coat of the bronchus and send penetrating twigs to the submucosa Probably the framework of the alveoli is supplied by these systemic arteries

The medial pleura is supplied directly from the annulus whereas the anterior, lateral and interlobar visceral pleura are supplied by bronchial arteries emerging from lung substance.

The Bronchial Veins

There are two separate systems of bronchial veins. The true bronchial *veins drain* the intrapulmonary bronchi and the supporting interstitial framework of the lung. The pleurohilar veins drain the hilar structures and the subpleural planes of the lung The first drain into the pulmonary veins and the second into systemic veins such as the azygos, hemiazygos and interstitial veins.

The pleurohilar veins (Gilroy *et al*, 1951) communicate freely with the pulmonary veins both at the hilum and in the subpleural plane. The true bronchial veins course along a definite fascial plane which is an extension of the mediastinal perivascular fascia (Marchand, 1951). Situated within the plane between the bronchial wall and the peribronchial fascia lie the main trunks of the true bronchial veins, the true bronchial arteries and the lymphatics of the lung. The peribronchial fascia extends to the bronchioles separating the respiratory and interstitial portions of the lung. The latter is drained by the bronchial veins.

Applied Anatomy

A great deal of work has been done in studying the altered calibre of lung blood vessels in various experimental and diseased states. There has been considerable speculation about the anatomical paths taken by blood in a number of diseased states Discussion centres on the extent and site of anastomoses between the pulmonary and bronchial circulations and whether pulmonary artery blood can reach the left heart having by-passed the alveoli.

Cockett and Vass (1950) demonstrated in normal lung the existence of minute communications between the bronchial and pulmonary arterial systems and believe that, when for any reason the bronchial system enlarges, these communications dilate. In the experimental animal the greatest stimulus to enlargement of the bronchial system is complete occlusion of the pulmonary artery. The collateral flow from the aorta passes into the pulmonary artery radicles within the lung, thence through the lung capillaries and back to the left auricle via the pulmonary veins. The output of the left ventricle may under these conditions exceed that of the right by a third. The comparable situation in man is in congenital heart disease with pulmonary stenosis or atresia, and pulsating bronchial arteries may be seen radiologically in pseudo-truncus arteriosus.

In experimental pulmonary embolism, Ellis *et al.* (1952) have shown that the nutrient requirements of pulmonary tissue distal to an embolus can be met by the pulmonary arterial circulation through capillary anastomoses in the capillary bed The bronchial circulation is not necessary for this purpose, nor is it necessary for the development of infarction after embolism, provided sufficiently severe pulmonary "congestion" is present However, bleeding after pulmonary embolism may come from the bronchial circulation and the bronchial flow may promote the development of infarction after embolism

Liebow *et al.* (1949) report enlargement of the bronchial arteries and their anastomoses with the pulmonary arteries in bronchiectasis, but the stimulus for this is not clear. A possible explanation is that histological sections of bronchiectatic areas reveal large thrombosed arteries undergoing recanalization, and the obstruction may be sufficient to stimulate increased bronchial artery blood flow. That such an increased flow does exist is confirmed by finding more highly oxygenated blood in the pulmonary artery on the diseased side. Similar changes may occur in primary bronchial neoplasms, and Cudkowicz and Armstrong (1953) describe four cases of primary bronchial neoplasms in which there was a diffuse, proliferative bronchial arterial pattern extending to the tumour. It was not observed in two cases of metastatic lung tumours.

In absorption collapse of a lung or lobe after an initial short period of central cyanosis,

the arterial oxygen saturation becomes normal. There is, therefore, no flow of pulmonary artery blood past non-aerating alveoli, and it appears that the bronchial arteries produce a retrograde flow in the pulmonary system.

In contrast to experiments involving occlusion of a main pulmonary artery, Ellis *et al.* (1951) occluded the right posterior bronchial artery in dogs and found that this caused infarction and ulceration of the right stem bronchus and of the right lobar bronchi in the hilar region. Distal to the hilum the bronchi remained normal. It appears, therefore, that under normal conditions pulmonary artery blood can maintain the integrity of the pulmonary tissue and the bronchial walls distal to the hilar region.

The evidence does suggest that shunting of blood can occur from bronchial to pulmonary arteries in either direction distal to the hilum.

Arteriovenous anastomoses in the lung also probably occur, and in Meckel's *Anatomie* of 1820 it is said that "very important communications between the systems of red and blue bloods are found" Particular arteries which are "able to close" and are distinguished by their musculature have been described. It is said that they arise from a branch of the pulmonary artery and give rise to numerous arteriovenous anastomoses These lie in association with the bronchial venous plexus whose tributaries, as discussed, drain into the pulmonary veins. It is believed that the ability of these arteries to open or close governs the presence of a "through stream" which by-passes the alveoli.

Anastomoses within the lung venous system also seem to develop in various forms of chronic lung disease, notably emphysema, and the bronchopulmonary circulation is greatly expanded. There is considerable communication between the bronchial and pulmonary veins providing a by-pass in the event of occlusion of the latter. Liebow (1953) says that in their expanded state the bronchopulmonary veins constitute a shunt of significant size between the right and left auricles.

Another example of venous shunts has been suggested by Gilroy *et al* (1952). They observed dilated pleurohilar veins in mitral stenosis and pointed out that, as the pressure is higher in the pulmonary vein than the superior vena cava, the pleurohilar veins could constitute a method of modifying rises in pulmonary venous pressure.

The evidence, therefore, of anastomoses between pulmonary and bronchial arteries, pulmonary arteries and bronchial veins, and between pulmonary and bronchial veins is reasonably well substantiated.

Nerve Supply of the Lung Vasculature

The lung vessels are supplied by sympathetic and parasympathetic fibres which are woven into plexuses and carry efferent and afferent fibres. The sympathetic fibres arise in the second to the fifth or sixth thoracic ganglia They run mainly to the posterior pulmonary plexus, which lies in the posterior part of the hilar regions and also contains [illegible] distributed to the vessels bronchi, and glands of the lungs. This [illegible] bres The preganglionic fibres are the [illegible] They form synapses in the corres- [illegible] The post-ganglionic fibres are the axons of the ganglionic cells. The afferent fibres have their cell stations in the dorsal root ganglia of the upper five or six thoracic spinal nerves.

Preganglionic vagal fibres arise in the dorsal vagal nuclei. Afferent vagal fibres have their cell stations in the inferior vagal ganglia. Above the lung roots each vagus nerve divides and surrounds the root, forming a large posterior and a smaller anterior plexus. Below the roots there is union with sympathetic fibres from the oesophageal plexus and with vagal fibres from the opposite side. The lung vasculature is mainly supplied via the posterior pulmonary plexus which receives direct or indirect contributions from the upper thoracic sympathetic ganglia.

The autonomic nervous supply to the various lung vessels varies greatly in its richness. It is probable that the small bronchial arteries have the best supply, the pulmonary arteries are less well supplied, and the pulmonary veins are very poorly innervated. It has been remarked by many authors how generally poor the whole pulmonary vessel innervation is, especially when compared with the autonomic supply to the systemic vasculature.

There is no marked plexus formation round the pulmonary vessels, the nerves only winding round them and giving off branches at irregular intervals. Cookson (1953) has demonstrated frequent intercommunication by small bundles of fibres between the peri-vascular and peribronchial nerves, and he also showed, by special silver and methylene-blue stains, that there are comparatively few fibres around pulmonary capillaries.

Lymphatics of the Lungs

There is an abundant supply of lymphatics in the lungs which can be divided into a superficial and deep set. The superficial is contained in the pleura. The deep set accompanies the bronchi, and the pulmonary arteries and veins, and forms networks in the connective tissue septa. The two sets communicate in the hilum and in the pleura.

The pulmonary arteries are accompanied by two or three lymphatic trunks which are joined circumferentially by an irregular network. The pulmonary veins are surrounded in the same way and there are frequent communications between them, and those with the arteries and bronchi. Miller (1947) has pointed out that there are no lymphatics present in the walls of the air spaces distal to the ductuli alveolares and, therefore, there are no lymphatics in veins which arise from their walls.

The lymphatics of the pleura are arranged in irregular polyhedral rings which mark out the secondary lobules. Smaller lymphatics mark out the primary lobules. Distension of interlobular spaces by oedema fluid is of particular interest as it is seen so easily on X-ray plates (see Chapter 5).

There are very few valves in lymphatics within the lung, but they can be found in the hilum and pleural networks By studying the direction of the valves as well as by injection studies it is possible to have a general idea of the direction of lymph flow. The flow in the bronchial and arterial lymphatics is towards the centre of the lung. In lymphatics accompanying the veins the flow is towards the hilum. The valves in all these lymphatics point towards the pleura and hence there cannot be flow from the pleural lymphatics into the lung. Within the pleura lymphatic valves point in all directions and lymph probably circulates freely. The main trunk of the pleural lymphatics ultimately joins the pulmonary venous lymphatics at the hilum and enters the tracheobronchial lymph nodes.

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CHAPTER 2

PHYSIOLOGY AND HAEMODYNAMICS

By GRANT DE J. LEE

INTEREST in the physiology of the pulmonary circulation has been greatly stimulated by the impact of techniques enabling its study to be carried out in man himself. However, these investigations are often difficult to interpret because the techniques themselves are comparatively imprecise. In addition, serious difficulty arises in obtaining experimental control of the many variable and interacting factors which influence the pulmonary circulation. Thus, comparatively small changes arising in the pulmonary circulation itself may be masked by much larger changes occurring as a result of vascular changes in the systemic circulation, which may be influencing the lung circulation at the same time. More precise information may be obtained from observations on isolated lungs and from carefully controlled animal experiments But such studies may not be directly applicable to human physiology It is therefore unfortunately true to say that, although general principles of vascular behaviour within the human lung are recognized, the mechanisms controlling the pulmonary circulation in man are not precisely defined

The physiological alterations that can take place within the pulmonary circulation show great versatility. The main function of the lung is to permit efficient exchange of oxygen and carbon dioxide between the blood flowing through the lung capillaries and the air ventilating their related alveoli. This efficient gas exchange is possible over the full range of cardiac output, which may exceed 25 litres/min. under conditions of severe exercise. Yet it is accomplished although the capillary blood volume itself probably never exceeds 150 ml. In addition, the pulmonary vascular bed is characteristically a low pressure system and is capable of accommodating these wide variations in pulmonary blood flow with comparatively little alteration in pulmonary vascular pressure Furthermore, in disease, certain adaptations are possible which help to maintain normal gas exchange For example, adjustments of alveolar capillary perfusion may take place enabling the pulmonary blood flow to be directed to more normal areas of the lung and away from under-ventilated alveoli affected by disease

In the present chapter, the factors regulating the pulmonary circulation, and which help to maintain normal respiratory gas exchange, will be reviewed.

THE ANATOMICAL PROVISIONS AND SOME PHYSIOLOGICAL CONSEQUENCES

Pulmonary Capillaries, Arteries and Veins

The anatomy of the pulmonary circulation has been described in the previous chapter. The branches of the pulmonary artery which supply the air sacs of the lung divide into a

capillary network that envelops the alveoli and drains into the pulmonary veins. Electron microscopy reveals that the alveoli are lined with an uninterrupted layer of thin epithelial cells, which is separated by a fine, structureless, basement membrane from an equally thin single endothelial layer composing the capillary wall. This structural arrangement permits gas exchange by simple diffusion between the alveoli and the blood flowing through their capillaries. However, this same structure will permit transudation of plasma constituents into the alveoli if the capillary-alveolar pressure gradient were to exceed the plasma osmotic pressure at any time. Therefore, one vital requirement is that regulation of pulmonary capillary pressure must be such that this pressure is not exceeded, if pulmonary oedema is to be avoided.

Brenner (1935) has shown that the pulmonary arterioles and venules are structurally similar and difficult to differentiate unless they are seen joining their respective arteries and veins. They consist of endothelial tubes, surrounded by a single spirally-wound elastic fibril which appears continuous with the external elastic lamina of the parent artery Occasionally, the elastic fibrils split to enclose single muscle cells The pulmonary arteriolar wall thickness may compose only nine per cent of the total external diameter of the vessel compared with approximately 36 per cent in the case of the systemic arteriole. Again, the small arteries of the lung are much less well endowed with muscle fibres than their equivalent systemic arteries, while the larger arteries contain predominantly circular and again comparatively few muscle fibres The pulmonary veins have a media consisting of connective tissue and irregular elastic fibres, with scattered bundles of muscle throughout the media and a rather thick fibrous adventitia. The pulmonary vessels contain both sensory and motor nerve fibres at least as far as the alveolar capillaries (Larsell and Dow, 1933) In spite of their anatomical existence, the assessment of their physiological importance in the regulation of pulmonary blood pressure is still somewhat controversial and will need to be discussed in detail subsequently

The Bronchial Arteries and Bronchopulmonary Anastomoses

The bronchial arteries supply the bronchi only as far as the alveolar ducts, where the capillaries anastomose with vessels from the pulmonary artery proximal to the pulmonary capillary bed The bronchial arteries normally carry less than one per cent of the blood flow to the lung (Bruner and Schmidt, 1947). However, under conditions of disease, such as prolonged obstruction of a major pulmonary artery, bronchiectasis, or cyanotic congenital heart disease, an enormous increase in the bronchopulmonary anastomosis can take place. Fig. 1 is an illustration provided by the courtesy of Cudkowicz and Armstrong (1953) and shows the small number of fine bronchial arteries in a normal human lung which have been filled by injecting radio-opaque fluid at arterial pressures from the aorta in a cadaver. These are compared with the greatly hypertrophied bronchial artery supply shown in a similar injection specimen of a lung affected by bronchiectasis and lung fibrosis. Fishman and his colleagues (1958) have developed an ingenious modification of the Fick principle enabling them to measure the collateral blood flow occurring through the bronchopulmonary anastomoses in patients affected by various types of pulmonary and cardiac abnormality. Collateral blood flow up to eight per cent of the total pulmonary artery blood flow was obtained in some cases. The technique may well underestimate the total

collateral flow. However, these studies show that the bronchopulmonary anastomoses in disease may be quite large. The development of such anastomoses in conditions that lead to deoxygenated blood entering the systemic circulation serves a useful function, in

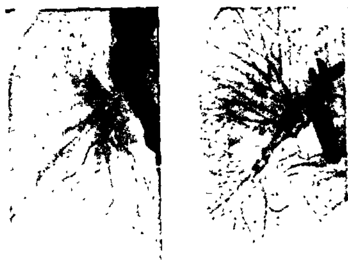


FIG 1 Lateral radiographs of lungs showing the bronchial art- [illegible]

Cudkowicz)

that they allow the blood to be presented for gas exchange to the alveoli for a second time (see Chapter 5).

Lymphatics

Pulmonary lymphatic vessels accompany the bronchial arteries as far as the lung atria. No lymphatic vessels can be demonstrated in the region of the lung alveoli. Drinker (1945) demonstrated a large increase in pulmonary lymph flow in the dog with pulmonary oedema. No direct measurements of pulmonary lymph flow have yet been possible in man. Such information would be of great value in providing a possible clue to the paradoxical association in some cases of mitral stenosis of very high pulmonary capillary pressures with freedom from clinical signs of pulmonary oedema It would seem possible that, if rapid lymphatic drainage occurred from the respiratory bronchioles, this might be great enough to prevent the accumulation of plasma transudate in the alveoli caused by the capillary pressure exceeding the plasma osmotic pressure in these cases. Lymphatic drainage in such cases is certainly suggested by the observations of Rossall and Gunning (1956), who correlated left atrial pressure measurements in man with the appearance of lymphatic lines on the radiograph of patients with mitral stenosis and pulmonary hypertension (Fig 2). They found that the radiological appearances of these lines occurred i

those cases whose left atrial pressures were in the region of 30 mm. Hg or more (see Chapter 5).

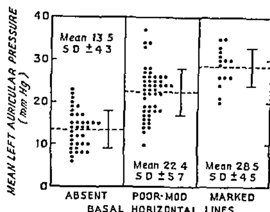


Fig 2 Relationship between basal horizontal lines on chest X-ray and left auricular pressure (By courtesy of A J Gunning)

The Distensibility and Capacity of the Pulmonary Vascular System

The distensibility of the pulmonary vascular bed has been measured under static conditions in animals by measuring the increased amount of blood that the lungs may be made to accommodate when the pulmonary veins are tied off The distensibility of the lung blood vessels varies with the species Thus, the dog's lungs show relatively small changes in pulmonary vascular pressure as the vessels are distended. Sarnoff *et al.* (1958) have also shown that under conditions of systemic vasoconstriction the dog's lungs may contain up to twice their normal volume of blood The pulmonary vascular system was also found to undergo stress relaxation, the pressure after injection of fluid being less in some records than it was immediately after injection

The volume of blood in the lungs has been determined using the Hamilton dye injection technique. The method does not allow a very precise volume to be measured and usually includes the heart volume. However, results show that the intrathoracic blood volume is about 20 per cent of the total blood volume, both in animals and man Changes in blood volume of less than 200 ml. cannot be detected by this method

A very small proportion of the intrathoracic blood volume is situated in the lung capillaries themselves Roughton (1945) estimated the volume of blood exposed to alveolar gas in the pulmonary capillaries He did this from *in vitro* studies of the rate of combination of carbon monoxide with suspensions of human red corpuscles at 37°C, combined with *in vivo* measurements of the rate of uptake of carbon monoxide per mm. Hg alveolar CO tension in the human being at high oxygen tensions. He found the normal pulmonary capillary volume was approximately 70 ml.

Recently, Roughton and Forster (1957) have carried out more precise calculations of the capillary volume At rest, the calculated capillary volume confirms Roughton's original figures. Studies under exercise conditions will be awaited with interest, although technical difficulties are likely to affect their accuracy. The distensibility of lung blood vessels at various flow rates will be considered in more detail in a subsequent section.

PULMONARY VASCULAR PRESSURE FLOW RELATIONSHIPS: PULMONARY RESISTANCE

Theoretical Considerations

The problems of haemodynamics are those of the flow of blood in a branching system of tubes of widely differing diameters and mechanical characteristics. The tubes vary in distensibility and a tension exists in their walls due to the blood pressure within. This tension is composed of three elements: the elastic recoil tension, "active" tension due to the contraction of smooth muscle, and surface tension at the blood-vessel interface. According to Laplace, there is a simple relationship between wall tension, vascular pressure and radius:

$$T = PR$$

where T = tension in dynes/cm. length of tube
P = pressure in dynes/cm²
R = equilibrium radius in cm.

Thus, at any given pressure, the tension of large vessel walls is very much greater than the tension of the walls of small vessels such as capillaries Some of the values for T, P and R in various blood vessels are shown in Table 1 taken from Burton (1951). He pointed out

TABLE 1
RELATIONSHIP OF PRESSURE, RADIUS AND TENSION IN BLOOD VESSELS
$(T = P \times R)$

Type of vessel	*Mean pressure mm Hg*	*dyne/cm²*	*Radius, R*	*Tension in wall, T, dyne/cm.*	*Amount of elastic tissue*
Aorta and large arteries	100	$1·3 \times 10^5$	1·3 cm down	170,000	+ +
Small arteries	90	$1·2 \times 10^5$	0·5 cm.	60,000	+
Arterioles	60	8×10^4	0·15 cm. – 6 μ	1,200 – 500	±
Capillaries	30	4×10^4	4 μ	16	0
Venules	20	$2·6 \times 10^4$	10 μ	26	0
Veins	15	2×10^4	200 μ up	400	+
Venae cavae	10	$1·3 \times 10^4$	1·6 cm	21,000	+ +

After Burton (1951)

that, under conditions of "active tension" due to contraction of smooth muscle (or to an interface tension between blood and the endothelial wall), there is an unstable equilibrium within the blood vessel, so that any slight departure from the point of equilibrium

those cases whose left atrial pressures were in the region of 30 mm. Hg or more (see Chapter 5).

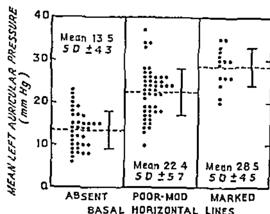


FIG 2. Relationship between basal horizontal lines on chest X-ray and left auricular pressure. (By courtesy of A. J. Gunning)

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The expression $8\eta L/R^4$ represents the resistance (R) offered to flow. Note that both viscosity and the dimensions of the tube contribute to the total resistance, and that it is evident that the mean linear velocity of flow (V) is proportional to the volumetric flow rate (Q), which in turn is proportional to the applied pressure P ($P=kV$). Thus a given change in applied pressure difference will produce a much greater change in mean linear flow velocity in a system with laminar flow than in one where turbulent flow exists.

In Newtonian liquids such as water, there is a straight line relationship between pressure (P) and flow (Q), which passes through the origin and whose slope is the resistance (R). For other fluids such as blood, anomalous viscosity effects appear at very low flow rates, so that the graph of P and Q becomes curved and intersects the pressure axis at a positive value, termed the yield pressure At high pressures, the normal straight-line relationship still applies. However, in the animal, Burton (1951) considers that the curvature of the pressure-flow graphs obtained in isolated perfusion experiments are due predominantly to the elastic structure of the blood vessels rather than to the anomalous viscosity of blood

Poiseuille's law is fundamentally inapplicable to a study of the intact pulmonary circulation, both because of the physical nature of the vessels themselves and also because the blood flow is pulsatile. However, until techniques for the continuous and simultaneous measurement of pulsatile flow and pressure are easily available, analysis of the phasic relationships of pulsatile pressure and flow will not be practical and stylized calculations of the relationships of mean vascular pressure to mean flow rates must serve as a useful comparison. Under such circumstances, Poiseuille's law serves to show that very small changes in the radius of a tube can produce considerable changes in the resistance to flow in that vessel.

Vascular Resistance in Isolated Lungs

Studies of isolated animal lungs perfused at measured flow rates allow calculations to be made on the effects of the distension of the pulmonary vascular bed on vascular resistance. These show that with increasing flow rates the pulmonary vascular resistance falls

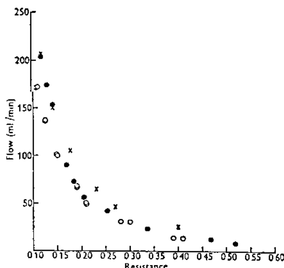


FIG 3 Flow-resistance curves on three isolated cat lung preparations
Resistance of pulmonary vascular bed $= \dfrac{\text{P A p} - \text{L A p}}{\text{Flow}}$
(By courtesy of H N Duke)

given by Laplace's law would result in closure of the vessel He coined the phrase "critical closing pressure" as the pressure existing within a vessel below which the active tension of the vessel wall will cause complete closure of that vessel This will be associated with a cessation of blood flow. The lung capillary closing pressure is probably in the region of 7 mm. Hg, for Borst *et al.* (1956) found that at left atrial pressures below this figure the pulmonary artery pressure and left atrial pressures were not equal at a time when there was no blood flow through the lung. This suggested that the lung capillaries between them had closed

In a hydraulic system, two types of flow behaviour exist: streamlined and turbulent flow. In man, it is probable that turbulent flow only exists in the heart chambers, and pulmonary artery and aorta close to the pulmonary and aortic valves. In a large tube turbulence arises gradually as the flow rate increases Constrictions, or abrupt changes in tube radius, will tend to initiate turbulence. In a uniform tube, turbulence is likely to occur if the Reynold's number exceeds a certain value, depending on the nature of the fluid. The Reynold's number is given by

$$\mathrm{Re} \approx \frac{RV\rho}{\eta}$$

where R = tube radius (cm)
V = critical mean linear flow velocity (cm./sec)
ρ = density of the fluid
η = coefficient of viscosity of the fluid.

The Reynold's number for blood is found to be less than 1000.

In areas of turbulence, the applied pressure difference will vary with the square of the mean linear flow velocity ($P = kV^2$).

Streamlined or Laminar Flow

When a homogeneous fluid flows down a tube of uniform bore and small radius, the flow is streamlined Owing to the friction of the tube walls, the cross-sectional velocity is not uniform and a parabolic contour of velocity exists, the central or axial flow being fastest. The force to maintain this flow is measured as the pressure difference between the two ends of the tube

Poiseuille's law defines the relationship between pressure and flow for water in capillary tubes.

Thus:

$$P \propto \frac{8L}{\pi R^4} Q$$

where P = pressure difference across the system in dynes/cm²
L = length of tube in cm.
R = radius of tube in cm.
Q = flow in ml /sec.

Where fluids of different coefficients of viscosity (η) are used, a term for this variable must be inserted:

$$P = \frac{8\eta L}{\pi R^4} Q$$

pulmonary blood vessels are susceptible to nervous, humoral, or chemical control and whether this is active under normal physiological conditions.

Most meticulous control of the numerous variable factors influencing pulmonary blood flow must be undertaken if one is to obtain a reliable measurement of changes in pulmonary vascular resistance. No better examples of this are available than the many elegant studies of I. de Burgh Daly (1932, 1954, 1956), who devised experiments on innervated isolated perfused lung preparations of animals, chiefly dogs, to eliminate the effects on the pulmonary circulation produced by large passive changes in pulmonary blood flow, bronchoconstriction, and alteration in intrapulmonary pressure or bronchial vasomotor activity. These preparations were perfused at constant volume inflow or at a constant head of pressure with free outflow of blood from the left auricle. Bronchomotor effects were considered to be absent during nerve stimulation tests if the tidal air or ventilation overflow remained constant under controlled negative or positive pressure respiration respectively. In other experiments on whole animals with a widely opened thorax, the systemic vessels were also perfused at constant blood volume inflow To demonstrate the existence of pulmonary vasomotor nerves, both the sympathetic and parasympathetic nerves supplying the lung were stimulated, and pulmonary vascular responses were only regarded as proven if they could be demonstrated at zero systemic blood pressure and in the absence of any bronchomotor response (Fig. 4). The experiments showed that both vasoconstrictor and vasodilator fibres are present to the lungs, and pharmacological evidence suggested that the vasoconstrictor fibres were sympathetic in origin with cell stations in the stellate and middle cervical ganglia and that they possessed adrenergic post-ganglionic fibres However, in order to effect all the controls necessary, the conditions of the experiment became rather artificial This may possibly have led to some modification of normal responses, and makes it difficult to assess how important a factor such vasomotor activity may be in the control of pulmonary vascular resistance in the intact animal.

Daly and Daly (1959) have also studied the reflex effects on the pulmonary circulation when the baroreceptors in the region of the carotid sinus and aortic arch and the carotid chemoreceptors are stimulated. They used a vasosensory perfused living animal preparation in which the vasosensory areas of the carotid bifurcations and of the aortic arch, the brain, the remainder of the systemic circulation and the lungs were separately perfused Thus the problem was simplified as the secondary reflex effects on the pulmonary vascular bed arising from the sensory receptors in the heart and systemic circulation could be eliminated This enabled them to examine the primary reflex pulmonary vascular responses to stimulation of the vasosensory areas in the carotid and aortic regions Under conditions in which all known passive effects on the pulmonary vascular bed were excluded, including those due to the bronchial circulation, they found that carotid chemoreceptor stimulation produced pulmonary vasoconstriction, whereas stimulation of carotid and aortic baroreceptors caused pulmonary vasodilatation

Afferent fibres in the vagus nerves arising in the pulmonary artery, cardiac atria and ventricles have been described. These fibres probably provide the afferent branches of the pulmonary depressor reflexes by which veratrum alkaloids or a rise in pulmonary artery pressure produce slowing of the heart and a fall in systemic blood pressure Stimulation of afferent fibres from the left atrium has also been shown to cause a water diuresis by the kidney.

Carhill *et al.*, (1957) showed that when blood flow in the isolated perfused cat's lung was increased from 80–900 ml /min., the pressure gradient across the lungs increased with a linear relationship to the flow and to the volume of blood in the vascular territory perfused. Resistance did not change significantly in this range However, when the flow was reduced from about 30 ml./min. to zero, the vascular resistance increased sharply and the lung blood volume was also sharply reduced (Fig. 3) Perfusion with blood or saline produced similar results, suggesting that anomalous viscosity of blood was not an important factor.

When the left atrial and pulmonary venous pressure was first raised, the curved part of the pressure flow diagram disappeared The flow-pressure curve was much steeper than reported in the systemic circulation; flow changes in the cat of 100 ml./min. produced only 7 cm saline pressure change.

Similar effects can be demonstrated in isolated lungs of other animals and man. The practical suggestion that arises from this work is that large increases in pulmonary blood flow are accompanied by only small pressure increases, with a correspondingly small risk of pulmonary oedema developing at high flow rates.

Effect of Respiration on Vascular Resistance

Many investigators have shown both in the isolated lung and in the open-chested animal that pulmonary vascular resistance increases when the lung is inflated either under positive or negative pressure. Calculations of pulmonary vascular resistance in man at different phases of respiration are hard to obtain with accuracy but tend to confirm this observation. Inspiration will be accomplished by stretching the lung tissues The blood vessels, being among the structures involved, will also be stretched and will thus offer a greater resistance to blood flow In addition, with inspiration the intrathoracic pressure becomes increasingly negative At the phase of full inspiration, when airflow has ceased, atmospheric pressure will exist within the respiratory passages, including the alveoli There will thus be an increased pressure gradient from alveoli to lung tissues on inspiration, tending to close the small blood vessels of the lung This explanation for the increase in pulmonary vascular resistance on inspiration would tend to suggest that the pulmonary capillaries themselves may be acting as the resistance vessels of the lung.

Animal Studies in the Assessment of Pulmonary Vasomotor Activity

Some of the mechanical factors which affect lung resistance have been very briefly discussed in the previous pages, and their effects must be taken into account when any assessment of vasomotor factors controlling the pulmonary circulation is made. The

the body. The pulmonary circulation, on the other hand, has a blood flow which is secondary to the requirements of the systemic circulation, and which has less need for a mechanism requiring selective distribution of blood flow In the present section, some of the evidence obtained from animal studies will be examined to consider whether the

The Effects of Hypoxia

Interpretation of the effects of hypoxia upon the pulmonary circulation tends to remain confusing as the evidence, even from careful animal studies, is contradictory. For this reason, even at the risk of some repetition in subsequent chapters, it seems important to consider evidence from animal studies on which our knowledge of the action of hypoxia is based. They will indicate some of the difficulties that arise when attempting to obtain evidence of the action of hypoxia even when carefully planned animal experiments are possible. von Euler and Liljestrand (1946) showed that the pulmonary artery pressure rose in cats breathing low concentrations of oxygen. These observations were confined to pressure measurements only and thus no conclusions regarding the pulmonary vascular resistance could be made.

However, studies of unilateral hypoxia in the rabbit and the dog have shown a shift of blood away from the hypoxic lung, indicating a rise in pulmonary vascular resistance with hypoxia. This suggests that vasoconstriction due to hypoxia could provide a mechanism whereby blood is diverted from poorly ventilated to better ventilated parts of the lung. Investigation of such a mechanism is complicated by the action of hypoxia in other parts of the body. Hypoxia often causes a rise in cardiac output, it may increase bronchomotor tone, and alter the left atrial pressure. All these factors have been shown to cause secondary alterations in pulmonary vascular resistance. In addition, hypoxia may stimulate the release of adrenaline. Evidence of hypoxic vasoconstriction has been obtained by many workers who have shown a rise in pulmonary artery-left atrial pressure gradient with little rise in cardiac output. However, Aviado *et al.* (1957) have recently carried out a series of experiments where pulmonary vascular pressures and pulmonary blood flow were measured and concluded that at least four opposing factors were involved in producing the variable effects of hypoxia that may be encountered. They were able to demonstrate powerful reflex pulmonary vasoconstriction from hypoxic stimulation of chemoreceptors in the carotid and aortic bodies. Some of the conclusions did not agree with those made by Daly and Daly (1959) quoted in the previous section. This may be due to superimposed systemic vascular effects, as control of events outside the pulmonary circulation itself was not undertaken in the same careful manner that was possible in the Dalys' studies. But the local effects of hypoxia studied by ventilating an isolated lobe with reduced oxygen produced the opposite effect, namely vasodilatation. Passive reduction in pulmonary vascular resistance could also take place as a result of the rise in pulmonary blood flow caused by hypoxia. However, this effect, too, may be opposed by the vasoconstrictor effect due to the release of adrenaline.

The Site of Action of Hypoxia on the Pulmonary Vessels

The local dilator effect of hypoxia found by Aviado is not confirmed by others. During constant volume inflow experiments in both cat and dog, Duke (1954, 1957) has shown a rise in pulmonary artery pressure in response to inhalation of reduced oxygen gas mixtures. This response was similar in duration and latency to that occurring in isolated perfused lungs and it was independent of changes in left atrial pressure. In her perfusion studies of isolated lungs, similar responses were obtained whether the lungs were perfused with venous blood from pulmonary artery or pulmonary vein. These reversed

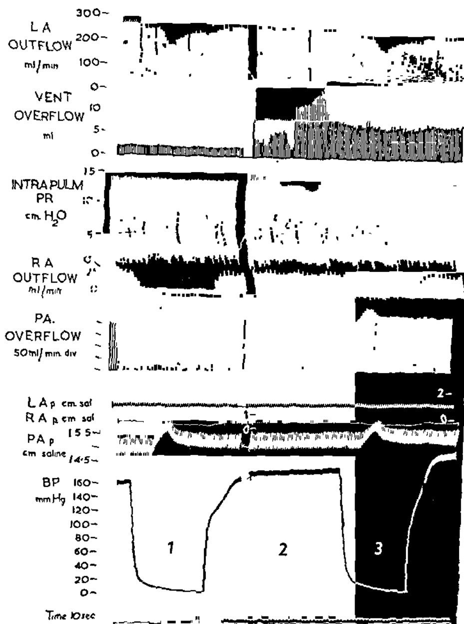


FIG ... nchial cir- ... pulmonary ... ventilation

... m sec /20 ... idal air = 58 ml

(2) Inspiratory pressure reduced in steps from 14 5 to 12 5 cm H_2O, then increased to 13 5 Expiratory pressure throughout 2 5 cm H_2O The P.V.R. ...

The P.V.R. increased by 35 per

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perfusion experiments suggested to her that the site of hypoxic vasoconstriction may be the lung capillaries themselves.

The Effects of Carbon Dioxide

Studies in the isolated animal lung and also in the living animal show that concentrations of five to ten per cent carbon dioxide in the inspired air increases the pulmonary vascular resistance. These effects are not abolished by dehydroergotamine, atropine or vagotomy. Some evidence exists that hypercapnoea shunts blood from the hypercapnoeic lung, but the study of the pulmonary vascular effects of carbon dioxide have not been studied either in animals or man to nearly as great an extent as the effects of hypoxia Neither has the possible potentiating effect of combined hypoxia with carbon dioxide retention received any careful study.

THE STUDY OF THE PULMONARY CIRCULATION IN MAN

The previous sections of this chapter have set out to review the mechanical, reflex and chemical factors known to influence the pulmonary vascular bed in the animal, where carefully controlled experimental study of their action is available. In summary, it may be said that mechanical factors such as the level of left atrial pressure, volume of blood flow, distribution of pulmonary blood volume, and degree of inflation of the lungs, will produce quite large changes in pulmonary vascular resistance. Reflex vasomotor control of the pulmonary circulation can also be demonstrated experimentally, but these experiments require very careful control, necessitating elaborate preparation of the animal. It is therefore difficult to assess the relative importance of this factor *vis-à-vis* the secondary effects resulting from the mechanical factors mentioned and also from more powerful vasomotor changes taking place simultaneously in the systemic circulation. Hypoxia and carbon dioxide retention can also cause both reflex and local pulmonary vasoconstriction in addition to changes in cardiac output

The interrelationship of these various factors may be so complex that in the intact animal or man there is little possibility of assessing their relative importance. Thus, investigation of the pulmonary circulation in man cannot offer any hope of the same precision for study, and only heavily qualified statements regarding its function are possible The problems are further complicated by the relative inaccuracy of techniques available for use.

Techniques available for the Study of the Pulmonary Circulation in Man
Measurements of Pulmonary Blood Flow and Cardiac Output
The Fick Principle

Estimation of cardiac output by the direct Fick principle is now such a commonplace procedure in the clinical investigation of the circulation that it is as well to examine the requirements needed for its accurate application. If the Fick principle is to be used in determining blood flow through an organ such as the lung, it is necessary to measure a substance which is added to the blood during its period of flow through the organ. The

amount which is added to the organ by the blood flow is equal to the difference between the amount brought into the organ and the amount carried away from it.

An amount of material in the blood can be expressed as a concentration multiplied by a volume:

$$\frac{dN}{dt} = F_i \times C_i - F_o \times C_o \tag{1}$$

where dN = amount of material added to the blood during time interval dt
F = blood flow into the organ
F_o = blood flow out of the organ
C_i = concentration of reference substance flowing into organ
C_o = concentration of reference substance flowing out of organ.

Equation (1) only refers to instantaneous periods of time and therefore one must examine the conditions in which it can be integrated and solved for blood flow. Integration requires that $F_i \times C_i$ and $F_o \times C_o$ are continuous factors of time (t), and it is usually assumed that $F_i = F_o$ is constant over the period of study and that this is equal to the mean blood flow through the system. Now, if this constancy is not true, and in a pulsatile system of blood flow it never can be true, an error will develop from making such an assumption.

The standard Fick equation embodying this assumption is.

$$F = \frac{Q}{C_o - C_i} = \frac{Q}{\Delta C} \tag{2}$$

$$\text{or, Cardiac output } (F) = \frac{\text{Oxygen consumption } (Q)}{\text{Arteriovenous } O_2 \text{ difference } (\Delta C)}$$

Visscher and Johnson (1953) have mathematically analysed the errors, taking two successive finite intervals of time, and assuming that during each time period each flow and concentration difference of the reference substance remains constant, being designated F_1, ΔC_1, F_2 and ΔC_2, respectively. They obtained the following equation.

$$F_1 \Delta C_2 + F_2 \Delta C_1 = F_1 \Delta C_1 + F_2 \Delta C_2 \tag{3}$$

$$\text{or } F_1 (\Delta C_2 - \Delta C_1) = F_2 (\Delta C_2 - \Delta C_1) \tag{4}$$

which indicates that only when $F_1 = F_2$ or $\Delta C_1 = \Delta C_2$ will the mean values for F (cardiac output) and ΔC ($A - V$ oxygen difference) apply. In the body this cannot occur, since the pulmonary blood flow is pulsatile and since the rate of oxygen uptake into the pulmonary capillaries is influenced by the cyclical character of ventilation and can only be measured at the mouth rather than at the alveolar capillary membrane. In addition, the blood samples required for the determination of the oxygen content of blood entering and leaving the lungs are averaged with respect to *time* rather than to *volume*, as they are collected at a constant rate while the volume of blood flow is varying because of the pulsatile nature of the cardiac output. These theoretical considerations, however, do not introduce very large errors if certain precautions are taken to maintain a steady state of ventilation, cardiac output, and gas exchange. For practical purposes, this requires that the subject should maintain his physical state of exercise at a constant level for at least ten minutes before blood samples and simultaneous oxygen consumption measurements are made This is

a difficult criterion to fulfil in patients or under conditions of exercise and is practically never attainable when the short-term effects of drugs, such as ganglion-blocking agents, are being studied.

A particularly potent source of error in estimating cardiac output by the Fick method is the variation of blood flow occurring across intracardiac shunts The degree of shunt may vary very considerably due to alterations in the haemodynamics occurring with the phase of respiration, posture, etc. This will have large effects on the oxygen content of blood samples. Under normal circumstances, mixed venous blood samples giving a representative sample of venous return from both superior and inferior venae cavae may be obtained by sampling from the pulmonary artery by means of a cardiac catheter. Intracardiac shunts may be associated with streaming even as far as the pulmonary artery, so that it may be impossible to get representative mixed venous samples in such cases This error is in addition to the errors produced from the use of *time* averaged samples already mentioned. Finally, analytical errors in determination of blood gases and oxygen uptake must also be remembered. These errors are measurable and amount to ±15 per cent *It is salutory that in man one cannot rely on any greater accuracy for cardiac output* estimation than this Under such circumstances, it is not surprising that calculations of pulmonary vascular resistance in man are so often equivocal and contradictory

Dye Injection Techniques

Cardiac output estimation by the Hamilton dye injection technique has been shown to correlate well with the Fick method in the steady state. Fig 5 shows such a correlation The method depends on a known volume of dye (T1824) being injected as a bolus into the venous system. Timed arterial samples are collected from a convenient peripheral artery

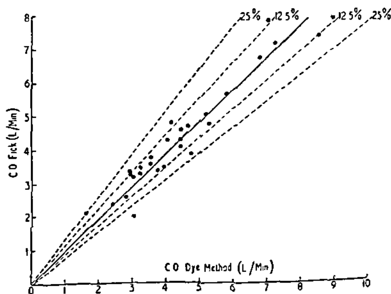


FIG 5. Comparison of cardiac output obtained by Fick and dye methods

and the blood analysed for dye concentration. The method depends on complete mixing of the injected dye with the blood flowing through the vascular bed between injection and sampling points. Sample analysis is tedious and modern modifications have employed the use of cuvette and ear oxymeters. These devices, though theoretically designed to give a linear response to changes in dye concentration occurring in the blood, often do not do so, and the clinical investigator is well advised to carry out a careful calibration of any new device of this type as the photocell responses vary individually.

One difficulty in calibrating dye concentration dilution curves obtained with the oxymeter depends on the use of a single mixed venous sample analysed photometrically which is correlated against the baseline shift in oxymeter tracing. Particularly with the ear oxymeter the deflection at such a point on the oxymeter tracing is often small, so that

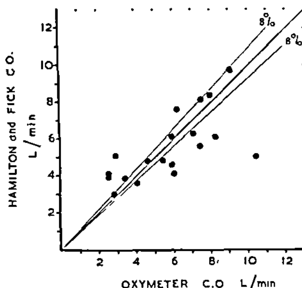


FIG 6a Simultaneous estimations of cardiac output obtained by Fick or Hamilton sampling methods compared with absolute ear oxymeter method

large calibration errors may be introduced Fig 6a shows a correlation of cardiac outputs obtained by the Fick and Hamilton blood sampling techniques compared with the cardiac output calculated by the ear oxymeter method Correlation is poor because of these oxymeter calibration artefacts However, if

or exe

tion is

another, provided identical dye doses are used at each estimation and provided the oxymeter sensitivity is kept constant Fig. 6b shows the same data as in Fig 6a expressed as percentage change of one subsequent cardiac output from the first. Calculations were made from the areas of the dye concentration curves in arbitrary units There is now excellent correlation with the Fick and Hamilton methods when using the oxymeter.

It has already been mentioned that estimates of the circulating blood volume may be

obtained between injection and sampling points, calculated from the product of the cardiac output and mean circulation time derived from the dye concentration-dilution curve. The method is not too versatile but allows changes greater than 200 ml volume to be detected. Thus, it has been possible to show that patients suffering from congestive cardiac failure associated with mitral stenosis have a smaller intrathoracic blood volume than

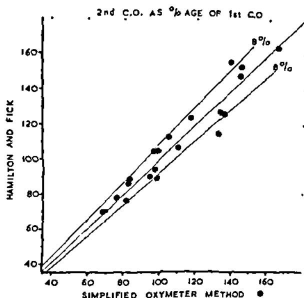


FIG 6b Comparison of percentage change in cardiac output obtained by the Fick or Hamilton sampling method, and the simplified oxymeter method

patients with left ventricular failure without valvular disease. The slope of the downstroke, associated with the onset of the appearance time of the dye curve, has been treated mathematically by several workers in an attempt to allow sophisticated calculations of lung blood volume and of the degree of valvular incompetence in patients with mitral valve disease. Too enthusiastic acceptance of such calculations are often made. This is not justified because in the case of valvular incompetence associated dilatation of cardiac chambers, especially the left atrium, also takes place This will also affect the slope of the dye curve and may affect the accuracy of the calculation of backward flow through the incompetent valve. This somewhat limits the practical usefulness of the technique as a diagnostic procedure for detecting valvular incompetence.

Intravascular Pressure Measurements

Direct measurement of intravascular pressures using electromanometers of various types is now standard practice The systemic arterial pressure is usually measured using a needle inserted percutaneously, while intracardiac and intrapulmonary vascular pressures are recorded using a radio-opaque plastic catheter. Pressures are recorded from an orifice situated at the tip or sides of the end of the catheter, which is placed in the required site under radiographic control. The use of long, pliable, slightly distensible catheters for

measuring pressures in this way may produce artefacts in the records obtained. The highest frequencies that need be recorded in a complex wave form such as the arterial pulse are not accurately known, but it is generally considered that instruments with a uniform sensitivity up to the tenth harmonic of the fundamental frequency of the pressure wave should be used. The pulse rate rarely exceeds 180 per min., so that a system with a uniform sensitivity from 0 to 30 cycles per sec. (c p.s.) should be adequate for recording intravascular pressures. Equally important criteria required of the manometer are that it should be stable and drift free, insensitive to temperature, humidity or movement, easily sterilized and easily filled with water or saline in such a way that it can be rendered bubble free. The manometer must have a linear response to pressure change. The effect of connecting a long plastic catheter to the manometer head is that the distensibility of the catheter introduces very considerable damping effects, so that the frequency response of the manometer may fall to near the fundamental frequency of the pressure to be measured. If this happens, resonance effects may occur and the pressure that is recorded may appear greater than the true pressure to be measured In general, a manometer with a stiff recording diaphragm will have a high natural frequency. Thus, the Hansen capacitance manometer has a natural frequency of approximately 100 c.p.s. When a No. 6F cardiac catheter 120 cm. long is attached to it, the damped frequency falls to 30 c.p.s., which is still satisfactory When using such a system, serious damping artefacts may be introduced if the system is not entirely free of bubbles. Where accurate pressures are to be recorded, the system should be tested for frequency response each time it is used. If it is found to be heavily damped, the system most probably contains an air bubble.

The response of a manometer to repeated exposure to the same pressure change at various frequencies should be determined for each device, so that its frequency response can be checked, and the errors from damping or resonance may be known By introducing electrical damping into the pressure recording circuit, the electrically integrated mean pressure can be obtained. The mean pressure can also be obtained from the continuous pressure curve by graphical integration or an approximate but satisfactory figure obtained by adding a third of the pulse pressure to the diastolic pressure.

Net Vascular Pressures within the Thorax

The centre of gravity within the body cannot be obtained practically, so an arbitrary manometer reference point must be chosen. This is often taken to be at the level of the sternal angle Another more accurate site is probably 10 cm anterior to the back, the chest A.P diameter also being measured, so that conversion to either reference point is possible. Variations in intrathoracic pressure will affect any vascular pressures recorded within the thorax. Thus, if the right ventricular pressure is 30/3 mm Hg and the intrathoracic pressure on inspiration is -7 mm. Hg, falling to 0 mm Hg on expiration, then the pressures recorded by the catheter will be 23/-4 mm. Hg on inspiration and 30/3 mm Hg on expiration. Accurate net pulmonary vascular pressures free of intrathoracic pressure variation may be obtained using a differential manometer recording the difference in pressure between the intravascular pressure and the intra-oesophageal pressure measured from an air-filled balloon or water-filled catheter in the oesophagus. The oesophageal site is used because it has been shown that the intra-oesophageal pressure is

very similar to the intrathoracic pressure, and is much more easily obtained as a practical procedure. Even today, the number of pulmonary haemodynamic studies performed in man using a differential manometer, so that the intrathoracic pressure can be eliminated as a source of variation, is still surprisingly small.

Two further sources of inaccuracy must be mentioned concerning recording intrapulmonary vascular pressures. First, under some circumstances the contractions of the heart produce very considerable movements in the catheter tip which may be seen under the fluoroscope to be moving to and fro in the pulmonary artery. These movements may produce very large pressure artefacts; they are usually quite easy to recognize but at times may be unavoidable. Other artefacts may occur even though the catheter tip appears stationary either because the tip is up against the vessel wall, which damps the tracing, or because ventricular contractions jar the length of the catheter within the right ventricle. Finally, in conditions where a high cardiac output exists, as in large left to right shunts associated with atrial septal defects, the systolic pressures recorded by a catheter in the main pulmonary artery and infundibular region of the right ventricle may be much lower than the systolic pressure in the cavity of the right ventricle. This might suggest the presence of an infundibular pulmonary stenosis, when it is actually due to artefact. This is due to the high blood flow through the pulmonary artery producing a negative velocity gradient at the catheter tip, which therefore behaves like a venturi tube (see Chapter 9). This artefact can be largely avoided by using a catheter with side holes at the tip.

Measurement of Pulmonary Arterial Pressure Gradients

Pulmonary arterial pressure gradients between main pulmonary artery and left atrium are required if calculations of resistance are to be made. The left atrial pressure may be obtained by direct puncture either through the back or via the transbronchial approach through a bronchoscope. However, numerous workers have been able to verify its surprising correlation with the pulmonary artery wedge pressure, measuring the left atrial pressure by the transcapillary approach. Using this technique, the pulmonary artery pressure gradient free of intrathoracic pressure variation can be obtained using a differential manometer and a double lumen catheter whose tip is wedged in a fine radicle of the pulmonary artery and whose second orifice is free in the main pulmonary artery. This technique is satisfactory in patients with near normal pulmonary vascular pressures. However, in patients with high pulmonary vascular pressures, the wedge pulmonary artery pressure may not record the left atrial pressure accurately, in which case direct left atrial pressure recording will be needed.

Calculation of Pulmonary Vascular Resistance in Man

Poiseuille's relationship for the estimation of vascular resistance (p. 12) may be modified to:

$$R = \frac{P}{Q}$$

where R = resistance
P = mean arterial pressure gradient
Q = mean blood flow.

This is calculated in man from:

$$\frac{\text{Mean PA pressure} - \text{mean left atrial pressure mm. Hg}}{\text{Cardiac output litres/min.}}$$

and may be expressed in simple R units or converted to dynes per sec/cm^{-5} using a density and viscosity constant for blood. This is neither strictly scientific nor necessary, and the simple resistance units give equal information. Normal pulmonary vascular resistance should not usually exceed 2·5 units and rarely exceeds one unit.

STUDIES ON THE PULMONARY VASCULAR RESISTANCE IN MAN

The difficulties encountered in attempting to measure either pressure or blood flow in the pulmonary circulation in man impose very great restrictions on the interpretation of the data obtained from such studies. It is unlikely that the combined errors of flow and pressure measurement in man are ever less than ±15–25 per cent of the true values Interpretation of resistance calculations based on such data are thus always likely to be equivocal, particularly as actual experiments suggest that pulmonary resistance changes often may not exceed such a figure. Quite apart from the technical errors inherent in the methods used, it is impossible to impose controlled flow conditions in man to enable one to obtain unequivocal evidence of changes in vascular resistance as is possible in animal studies This presents an enormous difficulty because nearly any procedure designed to test vasomotor function in the lungs simultaneously produces greater changes in the systemic circulation. For instance, posture and the phase of respiration will produce great alterations in systemic venous return to the right auricle with consequent changes in cardiac output. The same factors will also affect the volume of blood pooled in the systemic venous system, so that pulmonary vascular distension and consequent mechanical changes in pulmonary vascular resistance will occur. Attempts at studying the presence or absence of reflex pulmonary vasoconstriction by the use of ganglion blocking agents is a particularly potent source for misinterpretation Numerous studies have been published claiming to demonstrate release of reflex pulmonary vasoconstriction by the use of ganglion blocking agents in man. Even when doses are used that produce little change in systemic blood pressure, it is likely that large changes are produced in systemic venomotor tone. Under such circumstances, venous pooling in the systemic circulation would be associated with a reduction of lung blood volume, and on mechanical grounds alone might be expected to lead to an increase in pulmonary vascular resistance. In addition, the venous return to the heart will be affected, so that accurate measurement of cardiac output becomes vital Particularly under such conditions it becomes most difficult to obtain dependable data, so that interpretation of changes in vascular resistance is extremely difficult, as Goodwin *et al.* (1958) have recently pointed out. It was for this reason that Lee *et al.* (1954) attempted to study the relative importance of passive flow changes and reflex vasomotor activity in the pulmonary circulation. They did this by comparing the effective pulmonary artery pressure changes, using a differential manometer between pulmonary artery and oesophagus, with simultaneous changes occurring in the brachial artery under circumstances known to produce obvious systemic vasoconstriction. The use of Valsalva's manœuvre

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the brachial artery response in that pulse pressure changes were marked and varied considerably with the phase of respiration, being larger on inspiration than expiration. These [illegible]

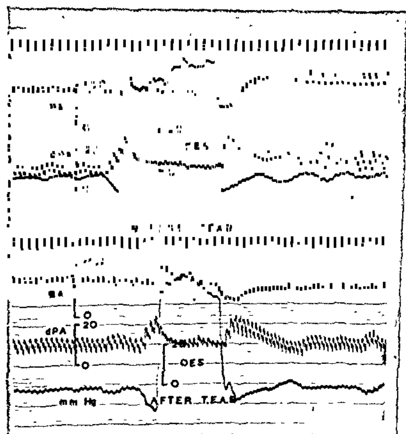
An intravenous dose sufficient to abolish the post-Valsalva vasoconstriction in the systemic artery was used. This had virtually no effect on the pulmonary artery pressure changes, suggesting that flow events were predominating. This was confirmed by similar events occurring in right atrial filling pressure. This study indicates that in normal man stroke volume changes appear to predominate in altering the pulmonary arterial pressure and that vasomotor changes are insufficiently active to produce changes demonstrable by the technique described. It may well be that when the pulmonary arterial system is converted from a low pressure to a high pressure system by disease, then vasoconstrictor effects may become important. This would explain the lack of response in normal subjects compared with the effectiveness of ganglion blocking agents in lowering the pulmonary artery pressure and resistance shown by Goodwin *et al.* (1958) and other workers in patients with mitral stenosis. This will be discussed more fully in Chapter 4.

In a short vascular system with apparently low vasotonicity, such as the pulmonary circulation, it would not be surprising if the pulsatility of blood flow through the main pulmonary artery still remained in the pulmonary capillary system also. This hypothesis has been tested and found to be correct. The method depended on a modification of Krogh's nitrous oxide technique for measuring lung blood flow in man, suitably modified to allow continuous and instantaneous flow events to be measured (Lee and Dubois, 1955). The subject sat in a closed body plethysmograph; the pressure within this chamber was measured continuously with a sensitive electromanometer. Events were timed against the subject's electrocardiogram After a control period, the subject took a breath of 100 per cent nitrous oxide and held his breath with the glottis open As the gas was absorbed from the lungs into the blood flowing through the pulmonary capillaries, the total volume of gases in the lungs, and hence within the plethysmograph, decreased producing a fall in plethysmograph pressure. Thus, a continuous record of nitrous oxide uptake was obtained (Fig. 8) From expired air samples and from the known solubility of N_2O in blood, the instantaneous pulmonary capillary blood flow rate was calculated (Fig 9)

The pulmonary capillary blood flow was found to be highly pulsatile. At rest, the peak blood flow rate was approximately 12 5 litres/min. This occurred at the time of the T wave on the electrocardiogram. The slowest blood flow occurred at the time of the QT interval and was about 3 litres/min After moderate exercise, the peak flow rate rose to approximately 28 litres/min., the slowest flow rate being about 6 litres/min. at this time.

These large changes in capillary blood flow rate with each heart beat suggest that the pulmonary capillary and arteriolar system must be very distensible The events are so rapid that some passive adjustment seems likely. For instance, the capillary volume might increase at peak flow rates because the closing pressure in certain areas of the capillary system was exceeded, so that opening of previously closed vessels took place. In these same areas at low flow rates the perfusion pressure would fall to less than the closing pressure and the capillaries would shut again In this way the pulmonary artery pressure could be controlled over a narrow range of pressure in spite of large changes in capillary

is a convenient stimulus for the purpose (Fig. 7). The brachial artery pressure changes were characteristic. During the period that the intrathoracic pressure was raised while Valsalva's manœuvre was maintained, there was an initial squeeze imparted to the thoracic aorta which produced a short-lived rise in arterial pressure. Then, as heart filling was impaired, the stroke volume decreased and pulse and mean pressures fell. With release of the Valsalva, the impaired venous return to the heart ceased and there was a rapid rise



Fig

in stroke volume. This was associated with a marked rise in both pulse and mean systemic blood pressure. This is sometimes termed the "overshoot". Part of this rise is due to an increase in stroke volume, but vasoconstriction induced during the period of low pulse and mean pressure is also responsible. This active vasoconstriction can be shown by a simultaneous decrease in the forearm blood flow at this time. In the pulmonary artery a similar rise in pressure also occurred following release of Valsalva's manœuvre. It differed from

using ^{15}oxygen suggests that oxygen uptake is approximately twice as large in the lower lobes as in the upper lobes in the erect posture (Hugh-Jones, 1959). This also could be explained on a similar basis because the pulmonary capillaries situated at the lung bases are kept open by the hydrostatic pressure from the left atrium. However, in the upper lobes the left atrium is below the lung capillaries, so that the left atrial pressure minus the hydrostatic pressure between atrium and upper lobe capillaries will be insufficient to exceed the capillary closing pressure in these lobes. The vessels will therefore remain closed until the pulmonary artery pressure rises sufficiently to open the vessels at high flow rates. Much further work is required in this field to remove this explanation from the realm of hypothesis.

Cournand (1950) has shown that initially the pulmonary vascular resistance decreases with increasing pulmonary blood flow. He and his colleagues studied the effects of increasing cardiac output on the pulmonary artery pressure during exercise in normal subjects and in patients with only one lung following pneumonectomy. In this way they were able to study the effects of a very wide range of blood flow rates through the lung in man. The pulmonary artery pressure did not start to rise above the upper limit of normal until the pulmonary blood flow exceeded approximately three times the resting flow rate. The absence of pressure rise in the face of increasing blood flow implies an expansion of the vascular bed, either by opening up new vessels or widening those that are already open, or a combination of both. Riley *et al.* (1954) have shown an initial linear relationship between the diffusing capacity for oxygen and the oxygen uptake. This linearity flattens out at high rates of oxygen uptake to give a maximum diffusing capacity, which takes place at levels of oxygen uptake very similar to those obtained by Cournand when the pulmonary blood flow became associated with a rise in pulmonary artery pressure above the normal range. Lilienthal and Riley (1954) suggested that there was a relationship between the critical level at which the pressure in the pulmonary artery increased significantly and the maximum oxygen diffusing capacity, which is a function closely related to the alveolar capillary volume. Such a suggestion implies that the alveolar capillaries themselves may be the site of peripheral resistance in the normal lung. This does not appear unreasonable in the light of the evidence of the existence of pulsatile capillary blood flow, which indicates that resistance to flow at the arteriolar level must be small.

Effects of Hypoxia on the Pulmonary Circulation in Man

So many studies of the haemodynamics of the pulmonary circulation in man are germain to our understanding of pulmonary hypertension that they will be discussed with greater benefit in Chapter 4.

However, it is appropriate to consider the effects of hypoxia in the present chapter and to remind the reader that the confusion that exists in our knowledge of its effects in man results from the large number of effects it produces both in the systemic and pulmonary circulation, which were shown by Aviado *et al.* (1957) in his studies in animals. If the pulmonary vascular resistance can be increased by local hypoxia or carbon dioxide retention, this action could provide an important mechanism for maintaining the most effective ratio of ventilation to perfusion throughout the lungs. Some of the most elegant studies of the effects of hypoxia in man have been carried out by Fishman *et al.* (1955)

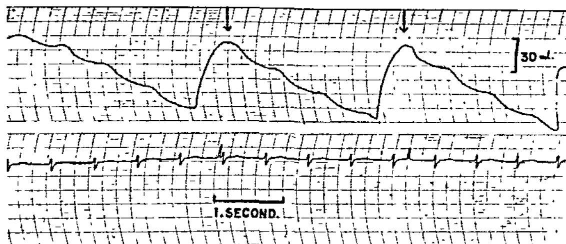


FIG 8 Record obtained during breath-holding after N_2O inhalation Plethysmograph pressure above, calibrated as volume change E C G below Plethysmograph vented to atmospheric pressure at the arrows

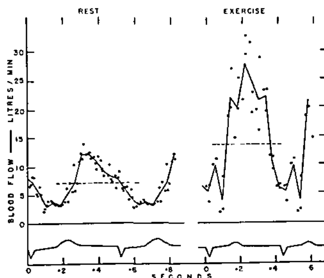


FIG ... blood flow rates at

put per minute

... blood flowing

conditions for oxygen would be maintained over a wide range of

Histamine. Most observers report a rise in pulmonary artery pressure after histamine but in many studies the cardiac output was not measured. Histamine produces only slight changes in the pulmonary circulation of the dog (Borst, 1957) but it produces a marked bronchoconstriction in most species and this could increase the pulmonary vascular resistance.

5-Hydroxytryptamine (Serotonin). One of the more occult functions of the lung is its part in the denaturing of humoral agents. The lung is one of the richer sources of mono-amino oxidase in the body. In cases of carcinoid tumour, a gradient in the content of 5-hydroxytryptamine can be shown between the blood levels of this substance found in the pulmonary artery and in the systemic arterial system, suggesting that inactivation has taken place in the lungs. Borst *et al.* (1957) have shown that 5-hydroxytryptamine has a powerful vasoconstrictor effect on the pulmonary vascular bed. This had been estimated as being some twenty times more powerful than nor-adrenaline. One of the interesting effects of this substance in cases of malignant carcinoid is its action in producing pulmonary hypertension.

Acetylcholine. Recently, acetylcholine has received great interest in its action on the pulmonary circulation in man, and some authors have claimed that this action indicates a release of reflex vasoconstriction In the animal, interpretation of its effects is difficult because acetylcholine produces bronchoconstriction, which may affect the pulmonary vascular resistance. Borst *et al.* (1957) concluded that acetylcholine had very little direct action on the pulmonary vasculature because only small and variable changes could be produced following its injection into the pulmonary artery.

Small doses of acetylcholine in man produce vasodilatation which is more marked in those patients in whom the pulmonary artery pressure is raised by disease or hypoxia. Fritts *et al.* (1958) have shown that the effect on the pulmonary circulation in man occurs equally well in the totally sympathectomized subject, indicating that the drug is acting directly rather than by releasing reflex vasoconstriction. Its action on the bronchial circulation to produce changes in pulmonary vascular resistance were considered unlikely as no changes in the systemic blood pressure occurred during infusion of the drug. At present, therefore, the use of acetylcholine does not really advance our knowledge of the mechanism regulating pulmonary vascular resistance. However, a long-acting compound with similar effects would be a very useful therapeutic agent in pulmonary hypertension

In conclusion, it may be stated that, although precise evidence is lacking, there is considerable presumptive evidence to suggest that in the normal animal and in man the pulmonary vascular resistance is regulated predominantly by mechanical and physical means. Hypoxia and carbon dioxide retention also appear to have some constrictor effects, which may be concerned with the regulation of ventilation/perfusion relationships within the lung. The part played by nervous control of the pulmonary vessels, although known to exist, is impossible to assess in the intact animal or in man at the present time. In disease, when organic changes in the vasculature of the pulmonary vessel walls take place, so that the pulmonary circulation is converted from a low resistance system to one of high resistance, apparently vestigal vasomotor reactions may assume greater importance This may well explain part of the confusion that exists in our knowledge of the function of the pulmonary circulation at the present time.

Using the techniques of bronchospirometry, cardiac catheterization, and peripheral arterial cannulation, they have applied the Fick principle to determine the blood flow through each lung simultaneously in man. The effects of unilateral breathing of hypoxic gas mixtures, known to increase the pulmonary artery pressure when applied to both lungs, could then be studied. If unilateral hypoxia were to increase the resistance of the hypoxic lung, then the blood flow should decrease in that lung and rise in the contralateral lung However, they found that concentrations of ten per cent oxygen given to one lung produced no alteration in the distribution of blood flow. Further work using much lower unilateral concentrations of oxygen will be awaited with very great interest. This may resolve the discrepancy between this work and some animal work where unilateral ventilation with nitrogen undoubtedly caused diminution of blood flow to the hypoxic lung. The rise in pulmonary artery pressure with moderate hypoxia which has been shown by others may be due to the combined effects of adrenaline release, rise in cardiac output, or reflex constriction from systemic chemoreceptors. Present experimental evidence does not permit us to answer these questions in normal man.

Effects of Drugs upon the Pulmonary Circulation in Animals and Man

Drugs that act on blood vessels can be divided into those which act through the autonomic nervous system or its nerve endings and those which, so far as is known, have a direct action on the vessels

Adrenaline and nor-adrenaline In animals, the action of adrenaline in perfused lungs, whether in the isolated state or in the intact lung, is almost uniformly vasoconstrictor But dilatation has been reported with small doses or when the initial vascular tone is high The constrictor effects of adrenaline are reversed by ergotamine. Since adrenaline usually causes bronchodilatation, which may itself reduce pulmonary vascular resistance, the vasoconstrictor action of adrenaline cannot be secondary to its bronchomotor action Experiments in the intact closed-chested dog have not demonstrated definite vasoconstriction.

In man, investigations of the effects of adrenaline have been inconclusive (Witham and Fleming, 1951).

Nor-adrenaline, on the other hand, appears to produce pulmonary vasoconstriction both in animals and man (Borst *et al*, 1957; Patel *et al.*, 1958)

Ganglion-blocking agents. The difficulties in interpreting data using these drugs in man have already been discussed earlier in this chapter. Further discussion on their use will be found in Chapter 4. The evidence of their action in the pulmonary circulation is conflicting

Aminophylline. Borst *et al* (1957) obtained evidence of a vasodilator effect in the pulmonary circulation of the dog, which has been confirmed by others. It also produces a rise in cardiac output. The complex cardiovascular responses in man make its action difficult to assess. The cardiac output usually rises and there is a fall in central venous pressure indicating myocardial stimulation. The fall in pulmonary artery pressure that may occur was shown by Werkö and Lagerlof (1950) to be associated with a fall in pulmonary transcapillary pressure and no fall in calculated pulmonary vascular resistance. This is contrary to other investigations in man, which have shown a fall in pulmonary vascular resistance using aminophylline.

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CHAPTER 3

PULMONARY FUNCTION AND CIRCULATION

By KENNETH W. DONALD

THE function of the lungs is to maintain normal and nearly constant oxygen and carbon dioxide tensions and content in the arterial blood in all physiological circumstances without causing any undue sensation of ventilatory discomfort or adverse effect on the heart or any other organ. This constancy of the arterial blood gases in all degrees of activity and oxygen usage is maintained only by the efficient transfer of gas between the alveolar air and the blood passing through the alveolar capillaries Such a transfer demands the intimate bringing together of blood and gas and the maintenance of an adequate gas-tension gradient between them. It is the function of ventilation that maintains and freshens the alveolar gases despite the constant interchange of oxygen and carbon dioxide with the venous blood This ventilation must not only be adequate in total quantity but must be efficiently distributed to all alveoli through which blood is flowing. Similarly the venous blood from the right heart must be efficiently distributed to all ventilated alveoli In this way an enormous blood-gas interface is created. Any lack of correlation between the ventilation and circulation of the lungs, in the form of ventilation of unperfused alveoli or perfusion of underventilated alveoli, will mean wasted ventilatory effort or imperfect oxygenation of blood and will cause a reduction in the effective blood-gas interface Finally there must be no undue impedance to the diffusion of gases through the structures present between the alveolar gases and the blood

The term respiratory failure is used in many different ways and is obviously a matter of definition. If a patient suffers ventilatory discomfort (dyspnoea) either at rest or on exercise, then, strictly speaking, this constitutes some degree of respiratory failure. Such wide use of the term would decrease its value in clinical medicine. The definition used by most respiratory physiologists is that respiratory failure is present when the arterial blood oxygen tension falls below or the carbon dioxide tension rises above the normal limits during any degree of activity. However clinicians reserve the use of this term to conditions where the arterial blood oxygen content is becoming so low at rest that life is threatened, and this is a reasonable and useful convention Respiratory failure, used in the clinical sense, may be caused by the failure of the respiratory centres due to poisons, ischaemia or severe hypoxaemia. It may be caused by the paralysis of the respiratory muscles due to poliomyelitis, myasthenia gravis or other neuro-muscular diseases. It may be caused by defective alveolar ventilation due either to obstruction of the respiratory passages (angioneurotic oedema, status asthmaticus, severe acute bronchitis) or an acute reduction in the amount of functioning lung (severe pneumonia, gross collapse including

bilateral pneumothorax) or a combination of the two (bronchitis and bronchopneumonia with previous lung damage or emphysema).

The function of the heart is to pump adequate quantities of blood to the lungs and body while maintaining low normal pressures behind the ventricles in all physiological circumstances. Ventricular failure, either right or left, occurs in two stages. Firstly there is an increase in the diastolic intraventricular pressure owing to the inability of the ventricle to empty adequately during systole. The atrial and pulmonary or systemic venous pressures will therefore become elevated although flow may be maintained at normal levels. In the second stage of failure the output of the ventricle will fall, first on exercise and later at rest.

In a number of lung diseases, the right ventricle performs increased work. This is usually due to the development of increased pressures in the pulmonary artery. In patients with hypoxaemia and carbon dioxide retention the cardiac output may also be somewhat elevated and further increase the right ventricular work Right ventricular hypertrophy and finally failure may result. These patients appear unable to initiate any circulatory economy by a reduction of blood flow to skin and other organs because of the potent vasodilating effects of hypoxaemia and hypercarbia

Respiratory and right ventricular failure caused by lung disease can occur quite separately although either may help to precipitate the other. Respiratory failure will contribute to heart failure by the adverse effect of reduced myocardial oxygen tensions and the increased cardiac work due to further pulmonary hypertension and increased flow Right ventricular failure with a reduced cardiac output in the presence of moderately severe hypoxaemia will render the vital respiratory centres even more hypoxic and thus cause central respiratory failure. However a patient may be in severe respiratory failure without right ventricular failure and this is not infrequent in pulmonary emphysema Similarly a patient with lung disease may develop right ventricular failure of a severe degree without respiratory failure An excellent example of this is found in certain patients with scleroderma where the vascular obstruction in the lung may be far greater than the interference with ventilation, gas distribution and gas transfer Although it is the right ventricle that is embarrassed in lung disease, the proper functioning of the lungs is dependent on a normal left ventricular function. If this fails and there is a rise of pressure in the left atrium and pulmonary vasculature, then lung function is grossly disturbed. Mitral stenosis will also cause a rise of pulmonary vascular pressures and disturbance of lung function.

Lung Volumes

The gas volumes in the lung at the end of quiet expiration, during full inspiration and full expiration are known as the functional residual capacity, the total lung capacity and the residual capacity respectively The vital capacity is the maximum volume of gas which can be expired after a maximum inspiration (see Fig. 10) In a young healthy person the vital capacity is about four-fifths of the total capacity. This fraction of the total capacity which can be filled and emptied by maximum respiratory effort is limited by the rigidity of the thorax and the collapse of small airways when violent expiratory pressure is exerted on the lungs. The vital capacity and its components can be determined by simple spirometry The residual or the functional residual capacity can be measured by the degree of dilution of a measured volume of inert gas (usually helium) when the patient is breathing

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into a spirometer system of known volume. These "static" lung volumes are not accorded the same significance as previously.

In asthma and bronchitis with varying degrees of pulmonary emphysema (chronic obstructive respiratory disease) the total lung capacity is unaltered or slightly increased. The lung volume at the end of quiet expiration (functional residual capacity) is increased owing to impaired lung recoil, increased expiratory resistance and bronchiolar collapse or narrowing. *Owing to the same factors the fraction of the total capacity that can be expired* by maximal effort (vital capacity/total lung capacity) is greatly reduced and may be of the order of 0·5 instead of 0·75. Thus the vital capacity is small and the residual lung capacity large. However similar changes in the lung volumes may occur with increasing age and with bronchial obstruction without parenchymal degeneration (pulmonary emphysema) and therefore these changes are not a precise measure of the degree of permanent

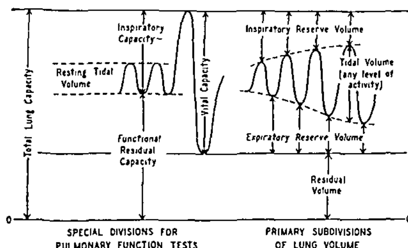


FIG 10 Diagram to illustrate agreed standardized terminology of the subdivision of lung volume (Pappenheimer) All gas volumes to be corrected to body temperature, pressure and saturated with water vapour (B T P.S)

lung damage or of total lung function. In uncomplicated diffuse lung fibrosis and in heart disease, the residual capacity is normal and the total lung capacity and vital capacity are reduced.

Ventilatory Capacity

The ventilatory efficiency of the lungs can be measured by the determination of the volumes ventilated during maximum voluntary ventilatory effort over 15 sec. (maximum breathing capacity). This is a highly unphysiological procedure and gives only a wide overall measurement of many combined factors (patency of airways, compliance and recoil of lung and chest wall, muscular efficiency). The maximum expiratory velocity or the volume expired over a short period (0·75 sec) can be measured by various low resistance circuits and electrical timing devices and these values correlate well with the maximum breathing capacity. They are useful in so far as their performance is shorter, involves less effort and is less dangerous in the presence of lung infection. The maximum ventilatory

capacity is reduced in any condition where there is increased airway resistance (asthma, bronchitis, emphysema), decrease of lung recoil (emphysema), decrease of lung compliance (severe fibrosis, heart disease), gross chest or lung deformity (kyphoscoliosis, thoracoplasties), diaphragmatic or respiratory muscle weakness or paralysis (phrenic nerve damage, neuromuscular disorders) or increased inertia of body tissues moved by respiration (intrathoracic or abdominal tumours or fluid including pregnancy, extreme adiposity) Although the maximum ventilatory capacity is an important measurement of the efficiency of the lungs as regards total ventilatory function, it does not in any way measure efficiency of gas distribution or gas exchange.

Gas Distribution

The efficiency of distribution of the tidal air which passes the dead space to the alveoli of the lungs is determined by many techniques. In the healthy normal subject the equality of distribution of gases throughout the lungs is remarkable. It is considerably disturbed by anaesthesia, any undue distortion or restriction of the chest wall, abnormal respiratory behaviour (deliberate changes of lung volumes or rhythm) and probably by violent exercise. The rate of washing out of nitrogen from the alveoli during oxygen breathing in an open circuit or the rate of mixing of helium or any inert gas in a closed circuit is largely a function of distributional efficiency (correction is made for the rate and depth of breathing and the volumes involved). The rapid serial analysis of the tidal air by near-instantaneous gas analysis with or without a previous breath of oxygen or an inert gas (helium) also gives important information concerning gas distribution and equality of alveolar ventilation. Nitrogen, helium, oxygen and carbon dioxide meters are used and the mass spectrometer allows the simultaneous estimation of four or more gases. The reason this serial technique can be effectively employed for this purpose is that if spatial distribution is impaired then the less well ventilated alveoli empty later in expiration. If carbon dioxide and oxygen tensions are being measured, then the carbon dioxide tension will be higher and the oxygen tension lower towards the end of expiration if gas distribution is faulty.

In patients with chronic obstructive respiratory disease there is a marked delay in the rate of nitrogen wash-out during oxygen breathing, a delay in mixing of helium in a closed circuit and marked changes in expired gas concentrations during a single expiration. These changes are, however, very variable with variable respiratory obstruction and cannot be reliably used to measure the degree of permanent lung damage. An attack of asthma or bronchitis, the breathing of an irritating gas or fog, or heavy smoking will also cause considerable but reversible alteration in the findings. In patients with lung fibrosis without chronic obstructive respiratory disease the evidence of impaired gas distribution is rarely very marked.

Work of Breathing

In recent years the actual work of breathing has been given considerable attention particularly in relation to the causes of impaired ventilatory capacity and the sensation of shortness of breath (dyspnoea). It has been shown that the intra-oesophageal pressure

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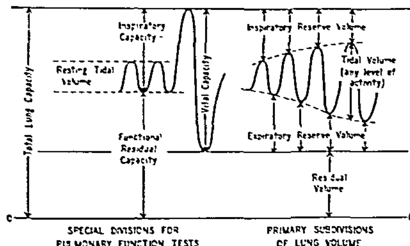


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Work of Breathing

In recent years the actual work of breathing has been given considerable attention particularly in relation to the causes of impaired ventilatory capacity and the sensation of shortness of breath (dyspnoea). It has been shown that the intra-oesophageal pressure approximates closely to the general intra-thoracic and intrapleural pressures. A thin air-filled rubber balloon is connected to a sensitive electromanometer by a thin plastic tube. The balloon and tube are easily swallowed and the intrathoracic pressures during respiration

are obtained with little inconvenience to the subject. The pressure gradient between the atmosphere and the pleural surface of the lungs can thus be studied with simultaneous measurement of the volumes passing in and out of the lung. The work performed in stretching the lungs ("elastic work") can be determined by measuring the volume inspired and the increase of pressure gradient from the beginning to the end of inspiration when there is no air flow. The pressure volume relationships can be easily plotted (almost linear). The added pressure gradient required to maintain air flow during inspiration and expiration can then be precisely determined, and if these are related to the simultaneous volume changes, then the work done in moving the gas through the air passages to the alveoli ("viscous work") can be calculated (see Fig. 11).

The elastic work is greatly increased in patients with increased pulmonary vascular pressures due to increased left atrial pressures (left ventricular failure, mitral stenosis). This reduction in lung compliance combined with the increased volumes ventilated may

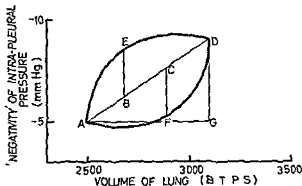


FIG 11 (Loop AEDFA) obtained when simultaneous changes in intra-pleural pressure and lung volume are related during a single respiration, curve AED being during inspiration and curve DFA during expiration. Line ABCD represents negative pres-

cause an enormous increase in respiratory work in heart disease. Because of this increased work by the respiratory muscles, the resting oxygen uptake may be increased by over one-third. The lung compliance is also reduced in severe pulmonary fibrosis or infiltrations. The smaller the amount of lung functioning, the more pressure change is needed to expand it a unit volume. This fact makes the accurate measurement of the lung compliance difficult if there is varied or extensive lung pathology. In emphysema the lung becomes increasingly less elastic and more compliant and thus the normal mean negativity of intrapleural pressure may be largely lost. However this is not always the case, as the ventilation of a decreasing fraction of the lung may demand increasing negative intrathoracic pressures despite a fall in the compliance of unit volume of lung. Further, there is almost always increased airway resistance, and abnormal negative and positive intrapleural pressures are generated during inspiration and expiration to move gas through the air passages.

The increase in viscous work is the most important disturbance in lung disease and is greatly increased in asthma and bronchitis with varying degrees of emphysema (chronic

obstructive respiratory disease) The increased resistance to air-flow both on expiration and inspiration is due to variable combinations of active bronchoconstriction (particularly in asthma) of mucous secretion and mucosal oedema. Expiratory flow is far more delayed than inspiratory flow. This is due to several factors. The elastic recoil of the lungs may be largely lost and thus rather inefficient and abnormal expiratory muscular effort must be used. The positive pressures generated outside the lung are transmitted to the alveoli round the bronchioles. As there is a sharp fall of pressure along the bronchiole the gradient across its wall becomes excessive and complete or partial collapse will occur. This air-trapping is one of the major features of chronic obstructive respiratory disease and it may be critically precipitated by a quite small further increase of airway obstruction It is likely that most of the so-called "bronchospasm" described in chronic respiratory disease is of this nature and not of bronchomotor origin. Patients with chronic bronchitis appear to have an extremely sensitive bronchial mucosa which becomes engorged in response to a wide variety of relatively mild chemical or physical stimuli. These stimuli, such as the breathing of fog or fumes containing irritating substances or even cold air, only affect normal persons if they are extreme. It is possible that the normal person shows similar mucosal reactions. The normal bronchial calibre and transbronchial pressure gradients would allow such congestion without causing undue respiratory obstruction or air-trapping. These considerations are, at present, the most feasible explanation of the expiratory wheezing (so-called bronchospasm) in the patient with chronic bronchitis during the winter in foggy industrial areas, and his lack of definite allergic reactions. Respiratory infections no doubt also play an important role.

The amount of respiratory work and the degree of negativity of intrapleural pressure have been carefully correlated with the sensation of dyspnoea. Although no precise relationship has been shown, almost all patients with dyspnoea have increased negative intrathoracic pressures on inspiration and are performing very considerably increased respiratory work.

Ventilation-perfusion Relationships

It has already been emphasized that to allow adequate gas transfer there must be efficient air and blood distribution in the lungs. A number of methods of measuring the efficiency of gas distribution have already been discussed The study of the distribution of the right ventricular output to the alveoli is, however, far more difficult. Histological and post-mortem injection studies have not given us a great deal of information Radiological studies of the regional changes of lung density due to blood flow or the regional pulmonary distribution of radioactivity immediately after injecting or inhaling radioactive substances are also methods still lacking in precision.

The most fruitful method of investigation has been the study of the gas tensions of arterial blood, which is almost identical in most instances to the mixed pulmonary *venous* blood Assuming, as yet, that there are no diffusional difficulties (transfer of gases between alveolus to capillary) let us consider the various effects of poor correlation of the alveolar

nd carbon dioxide tensions

(*b*) *Lung well ventilated and poorly or non-perfused.* High oxygen and low carbon dioxide tensions in both regional alveoli and regional pulmonary venous blood. Lung involved will act as increased dead space. Amount of blood involved will be small or nil.

(*c*) *Lung poorly or non-ventilated and poorly or non-perfused.* If change is proportional there may be normal gas tensions in regional alveoli and regional venous blood. In effect this constitutes almost non-functioning lung without any marked effect on dead space or blood gas tensions.

(*d*) *Lung poorly or non-ventilated and well perfused.* Low oxygen and high carbon dioxide tensions in both regional alveoli and regional pulmonary venous blood. It will be seen that two important disturbances can be easily identified by the study of arterial blood and expired gases.

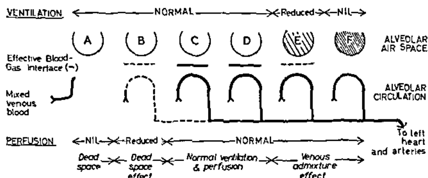


FIG.

If ventilated alveoli lack perfusion (*b*) there will be an increase in the dead space; that is, the amount of the tidal air not involved in gas exchange. Now normally the expired P_{CO_2} is not less than two-thirds of the alveolar P_{CO_2} as the dead space, in which air is unchanged is only one-third of the tidal volume For reasons given below, the arterial blood P_{CO_2} is used as a measure of alveolar P_{CO_2} and if the expired P_{CO_2} is less than two-thirds of the arterial P_{CO_2} (increased dead space) then the perfusion in certain parts of the lung is not commensurate with the ventilation.

If the ventilation of certain alveoli is ... (*d*) then the pulmonary venous and arterial blood w... tensions. Owing to the enormous capac... P_{CO_2} per unit change in carbon dioxide content) and possible changes in this capacity (a function of the buffering power), the level of the arterial blood oxygen tensions are

studied to detect alveolar underventilation. The rapid changes of oxygen tension, with small changes in oxygen content, in the upper ranges of the oxyhaemoglobin dissociation curve makes the study of arterial blood oxygen tensions particularly suitable for this purpose (see Fig. 13)

Assuming that there is complete equilibrium of oxygen between alveolus and capillary (as is almost always the case when breathing air, see below) than any depression of arterial oxygen tension below the alveolar oxygen tension is due to the perfusion of underventilated alveoli. The determination of the alveolar P_{O_2} is therefore necessary. In a normal subject the alveolar ventilation and gas tensions are almost uniform throughout the lung and an expiratory gas sample taken after the dead space has been washed out gives a reasonably representative figure. As previously explained, this state of affairs is no longer true in a patient with poor gas distribution as in chronic obstructive respiratory disease. The use of the

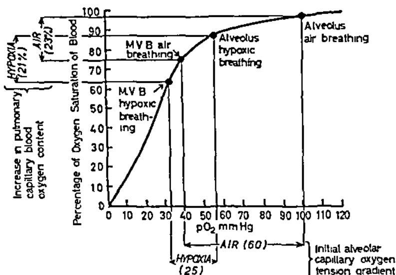


FIG 13. Oxy-haemoglobin dissociation curve relating tension of oxygen to percentage saturation (oxygen content). Note great change of ...

arterial P_{CO_2} as a measure of alveolar P_{CO_2} is an ingenious solution of this difficulty. Carbon dioxide is a highly diffusable gas and equilibration of blood and alveolar carbon dioxide is assured The final P_{CO_2} of blood leaving the lungs and entering the arteries gives an integrated figure representative of all the alveolar P_{CO_2} tensions of the lungs. Having a precise figure to describe the alveolar P_{CO_2} then the alveolar P_{O_2} can be determined by use of the "alveolar equation". This equation is a simple one and it is strongly recommended that the reader makes an effort to understand it as it is an essential part of even an elementary knowledge of modern respiratory function studies.

If the volume of gas entering and leaving the alveoli of the lungs is constant (V) then the total respiratory quotient (RQ) can be stated in the following terms:

$$RQ = \frac{CO_2 \text{ produced}}{O_2 \text{ taken up}}$$

$$= \frac{\text{Alveolar–inspired air } P_{CO_2} \text{ gradient} \times V}{\text{Inspired air–alveolar } P_{O_2} \text{ gradient} \times V}$$

$$= \frac{\text{Alveolar } P_{CO_2}}{\text{Inspired } P_{O_2} - \text{Alveolar } P_{O_2}} \qquad (\text{inspired } P_{CO_2} = \text{zero})$$

or, $$\text{Alveolar } P_{O_2} = \text{Inspired } P_{O_2} - \frac{\text{Arterial } P_{CO_2}}{RQ}$$

However, unless the RQ is unity there is a change in the volume of gas under consideration between its entering and leaving the alveoli. As the absolute amount of nitrogen is unchanged there will be a change in the fraction and tension of nitrogen present in the gas phase. This will cause a corresponding change of the fraction and tension of the other gases (oxygen and carbon dioxide). The appropriate correction for this change in volume is a function therefore of the RQ and the fraction of nitrogen in inspired air (0·79), thus

$$\text{Alveolar } P_{O_2} = \text{Inspired } P_{O_2} - \frac{\text{Arterial } P_{CO_2}}{RQ}[RQ + 0{\cdot}79 \ (1 - RQ)]$$

This equation, however, assumes that the gas exchange in each and every alveolus is representative of that in the whole lung or, in other words, that gas and blood distribution are absolutely equal throughout the lung The calculated alveolar P_{O_2} (sometimes called ideal alveolar P_{O_2}) is that which would obtain with a perfect lung and the gas tensions and respiratory quotients actually observed. As oxygen equilibration between alveolus and capillary has, for good reasons, been assumed, then the arterial blood oxygen P_{O_2} should be the same as the calculated alveolar P_{O_2} We thus have an arbitrary measure of what the arterial P_{O_2} should be if blood and gas distribution were perfect Any reduction below this figure (ideal alveolar–arterial P_{O_2} gradient or A–A gradient) is a measure of the underventilation of perfused alveoli. In a normal subject this A–A gradient is of the order of 5–8 mm. Hg and in a patient with severe emphysema it may be as high as 50 mm. Hg Thus even the normal lung is not quite perfect in this respect.

These findings can be described in another way which allows an easier mental image of the degree of disturbance It can be calculated (using blood oxygen content) what percentage of the blood passing through the lungs would be perfectly oxygenated (to ideal alveolar P_{O_2} level) and what percentage would be unchanged to give the arterial P_{O_2} and oxygen content actually found. The percentage of unchanged blood is called the "percentage venous admixture". This is a convenient way of integrating all grades of imperfect alveolar ventilation and blood oxygenation and can be considered as a functional shunt in contrast to an anatomical one. Even normal subjects may have up to about five per cent venous admixture, which is probably due to some degree of alveolar underventilation

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The analysis of arterial blood has been a great advance in respiratory physiology. The great clinical significance of carbon dioxide retention was not realized until this technique was used in clinical medicine. Arterial puncture if properly performed is neither painful nor dangerous. This country, with a strong bias to spirometric methods, has lagged greatly behind in this field and there are still too many workers who will resort to absurd stratagems to avoid arterial puncture Owing to the characteristics of the oxyhaemoglobin dissociation curve it is more accurate to measure oxygen tensions in the upper ranges and saturations in the lower ranges. Lilienthal and Riley (1954) therefore measure the arterial blood gas tensions by bubble tonometry and analysis in a Roughton-Scholander syringe This method, although it has many inherent and incurable errors, has been responsible for most of the advances in this field. Its place is now being taken by two much more accurate techniques The blood oxygen tension is measured by means of a platinum electrode guarded by a diffusible membrane. The blood carbon dioxide tension is measured by determining the pH of anaerobically separated plasma and of the same plasma after equilibration with other known carbon dioxide tensions. This latter technique still requires scrupulous care, particularly in the speed and temperature of plasma separation and also very accurate pH determinations.

Throughout this section it has been assumed that during air breathing the blood leaving the alveoli is in almost complete oxygen equilibrium with the alveolar gas, that any depression of the arterial oxygen tension below the calculated alveolar figure is caused by regional underventilation This assumption is largely true in the normal subject both at rest and on exercise. It is also true in the vast majority of patients with lung disease at rest, unless they are in severe respiratory failure with marked hypoventilation. This aspect will be elaborated in the section on diffusion.

Findings in lung disease. In patients with chronic obstructive respiratory disease there is evidence of gross disturbances of blood and gas distribution. The dead space (normally under 30 per cent) may be over 50 per cent. This means that a third of the gas normally entering well-perfused alveoli passes to portions of lung where there is no effective perfusion Similarly the percentage of venous admixture (functional shunt due to perfusion of underventilated alveoli) may reach levels of up to almost 50 per cent of the cardiac output In particular cases the increase of dead space and venous admixture do not go hand in hand. Some patients, particularly the less disabled, show a large dead space with little venous admixture and arterial desaturation This suggests that there is a regional reduction of alveolar perfusion without marked regional hypoventilation. In others, there may be a considerable increase of venous admixture with only a slight increase in dead space. This would suggest that regional alveolar hypoventilation is the predominant feature. Most severe cases show considerable but variable increases in both dead space and venous admixture. It has long been considered that chronic obstructive respiratory disease (loosely called pulmonary emphysema) has many different types of anatomical and functional disturbance and these findings would support this

Patients with diffuse pulmonary fibrosis (pneumokoniosis uncomplicated by massive fibrosis, lung distention or obstructive disease) show relatively normal dead space and

If the volume of gas entering and leaving the alveoli of the lungs is constant (V) then the total respiratory quotient (RQ) can be stated in the following terms:

$$RQ = \frac{CO_2 \text{ produced}}{O_2 \text{ taken up}}$$

$$= \frac{\text{Alveolar–inspired air } P_{CO_2} \text{ gradient} \times V}{\text{Inspired air–alveolar } P_{O_2} \text{ gradient} \times V}$$

$$= \frac{\text{Alveolar } P_{CO_2}}{\text{Inspired } P_{O_2} - \text{Alveolar } P_{O_2}} \quad (\text{inspired } P_{CO_2} = \text{zero})$$

or, $$\text{Alveolar } P_{O_2} = \text{Inspired } P_{O_2} - \frac{\text{Arterial } P_{CO_2}}{RQ}$$

However, unless the RQ is unity there is a change in the volume of gas under consideration between its entering and leaving the alveoli. As the absolute amount of nitrogen is unchanged there will be a change in the fraction and tension of nitrogen present in the gas phase. This will cause a corresponding change of the fraction and tension of the other gases (oxygen and carbon dioxide). The appropriate correction for this change in volume is a function therefore of the RQ and the fraction of nitrogen in inspired air (0·79), thus

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moderate increase of venous admixture. This accords with the slight arterial desaturation found in these patients.

The Diffusing Capacity

The true diffusing capacity of the lungs is easy to define and impossible to measure with complete precision. It is the amount of gas (usually oxygen is considered) that crosses the alveolar-capillary membrane per unit gradient of oxygen tension in unit time. This membrane is, in fact, a complex structure consisting of alveolar exudate, alveolar epithelium, interstitial tissue and capillary endothelium. In the usual methods of measurement, the impedance of the capillary blood plasma and red cell envelope and internal fluid to the passage of oxygen are also included The accessibility of reduced haemoglobin (a function of capillary blood volume, haematocrit and venous oxygen saturation) and the kinetics of the oxyhaemoglobin reaction all have a further effect on the values obtained. If these structures or factors are considered as serial impedances to the passage of oxygen from alveolus to haemoglobin molecule and the final combination with the haemoglobin, then the impedance of the true alveolo-capillary membrane is probably of the same order as the impedance due to plasma, red cell envelope and the finite rate of combination of oxygen and haemoglobin. Thus ordinary methods measure an apparent diffusing capacity which is about half the true diffusing capacity of the alveolar-capillary membrane In a normal subject (1·8 sq. m. B S.A.) the apparent diffusing capacity is of the order of 20 ml /mm. Hg/min. at rest (can be considerably higher, lower limit about 15), and increases over fourfold on severe exercise. As the normal resting oxygen uptake is of the order of 250 ml./min., the mean oxygen tension gradient between alveolus and haemoglobin is of the order of 13 mm. Hg.

Measurement. As the diffusing capacity is most intimately related to the state of the pulmonary circulation, it is worth briefly reviewing the methods of measurement.

Two-level oxygen method By consideration of the alveolar and blood oxygen tensions and knowledge of the mean gradient (see below) in normal subjects, Lilienthal and Riley (1954) showed on firm theoretical grounds that during air breathing the blood comes into almost complete oxygen equilibrium with the alveolus just over half-way through the alveolar capillary (see Fig. 14). The small alveolar-arterial blood oxygen tension gradient (up to 8 mm. Hg) in the normal subject is almost entirely due therefore to slight distributional defects, that is the slight underventilation of some alveoli (about three per cent venous admixture) If the normal subject breathes a lower percentage of oxygen (12 per cent) then a very different state of affairs obtains. Owing to the characteristics of the oxyhaemoglobin dissociation curve there is now a very much smaller initial oxygen tension gradient between alveolus and capillary blood (25 mm. in contrast to 65 mm. when breathing air) and the diffusion of oxygen is therefore slower (see Figs. 13 and 14) Further the blood has a far greater capacity for oxygen (small rise of oxygen tension per unit volume increase of oxygen content) at these low levels, and the oxygen tension rises more slowly during its passage through the capillary. Under these conditions therefore there is still a significant diffusion gradient between alveolus and capillary blood at the end of the alveolar capillary. As the blood oxygen tension changes far less with unit changes of oxygen content at these levels of oxygenation, the small normal venous admixture (three per cent) has no significant effect on depressing the oxygen tension of the blood leaving the lungs.

Thus in air breathing the alveolar-arterial gradient (about 8 mm Hg) is almost all due to distribution (venous admixture component) and a quite minute amount due to the diffusion gradient (membrane component) When breathing 12 per cent oxygen the alveolar-arterial gradient (about 6 mm.) is almost all due to the end-capillary gradient (membrane component) and a quite insignificant amount due to distributional defects (venous admixture component). If then the alveolar-arterial oxygen tension gradient is

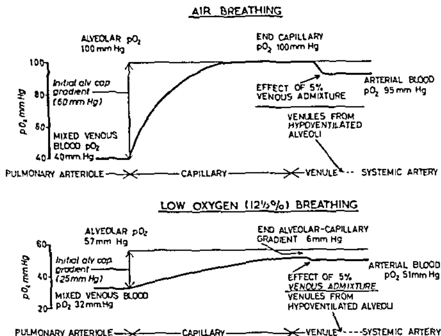


FIG 14 [illegible]

measured while breathing low oxygen mixtures, the diffusing capacity (apparent) can be easily determined·

$$\text{Diffusing capacity} = \frac{\text{Oxygen uptake}}{\text{Mean alveolar-capillary } O_2 \text{ tension gradient}}$$

The oxygen uptake is determined by spirometry, the alveolar oxygen tension by alveolar gas sampling or by the alveolar equation using the arterial P_{CO_2} and the mean capillary oxygen tensions from the initial (mixed venous blood P_{O_2}) and final (arterial blood P_{O_2}) pulmonary capillary tensions

In patients with lung disease it cannot be assumed, as in normal subjects, that either the venous admixture component or membrane component (final alveolo-capillary gradient) of the alveolar-arterial oxygen tension gradient is negligible at either level of oxygen breathing. The alveolar-arterial gradient is measured at two levels of inspired oxygen and

by use of graphs and trial and error, the only mean alveolo-capillary gradient (and thus diffusing capacity) and venous admixture values that will give the appropriate alveolar-arterial gradient (membrane plus venous admixture components) at each level of oxygenation are determined. The solution in each case is unique. This is an elaborate technique requiring considerable skill and special facilities. The levels of blood oxygenation have to be such as to cause considerable changes in the order of the membrane and venous admixture components of the A–A gradient. Further extreme hypoxia is to be avoided for the patient's safety and to ensure that there are not marked changes in ventilation and its distribution (venous admixture) or in the cardiac output (diffusing capacity) However, this method has been described in so far as it has greatly added to our knowledge of lung physiology and has a new and exciting future with the development of the more precise methods of blood-gas tension measurements previously mentioned.

Carbon monoxide techniques. In view of all these difficulties it is not surprising that workers turned once more to the early and apparently simple technique used many years ago by Marie Krogh (1915) In this method the subject breathed very low concentrations of carbon monoxide which is taken up by the haemoglobin with such avidity that its tension in the pulmonary capillary could be assumed to be zero. The patient's lung volume was determined and then he took one fairly large breath of a known carbon monoxide mixture The initial alveolar carbon monoxide concentration could be calculated from the degree of dilution of the known inspired volume in the known lung volume The breath was held for a number of seconds and then an alveolar sample was obtained after deep expiration As the fall in alveolar carbon monoxide concentration is exponential during the period of breath holding, the mean alveolar concentration could be determined from the initial and final values. As the capillary carbon monoxide tension is zero this figure is also the mean alveolar-capillary carbon monoxide gradient The amount of carbon monoxide absorbed over the period could also be calculated from the lung volume during breath holding and the fall in alveolar concentration. The diffusing capacity for carbon monoxide was then calculable. As the relative diffusion coefficients of gases are a simple function of solubility and molecular weight, the diffusing capacity for oxygen is easily determined Changes in diffusing capacity due to changes in lung circulation and lung volume during lung expansion and the transient apnoea have been shown to be unimportant in normal subjects

When this method is used to study patients with lung disease, certain difficulties arise The initial alveolar carbon monoxide concentration is no longer uniform throughout the lung alveoli owing to poor gas distribution (unequal alveolar ventilation) and both the deep inspiration and alveolar gas sampling afterwards pose further problems. Helium is used to measure, as it were, the effective ventilated volume and resultant dilution, but the diffusing capacity will still contain a distributional element when this value is used in the calculations A further difficulty is that the rate of combination of carbon monoxide and haemoglobin changes very considerably with different oxygen tensions. Although there will be lower carbon monoxide concentrations in poorly ventilated alveoli, the gas will combine more rapidly with the haemoglobin than at normal or higher oxygen tensions It is a nice example of scientific ingenuity that by studies at different levels of oxygenation this apparent difficulty is now being used to differentiate the true membrane diffusing capacity from the apparent diffusing capacity, which is influenced by the rate of combination of gas with haemoglobin.

The uptake of carbon monoxide during steady breathing has also been measured spirometrically and the alveolar tension of the gas determined by calculating the dead space from the arterial and expired P_{CO_2} and applying this figure to the expired P_{CO} The results of these techniques are also affected by poor gas distribution.

Diffusing capacity and exercise. It has already been stated that the diffusing capacity (apparent) increases with exercise. The precise causes of this rise are not fully known as yet. At the commencement of exercise the diffusing capacity rises at almost the same rate as the cardiac output and pulmonary blood flow It has been shown that the actual volume of blood in the pulmonary capillaries rises from resting values of 80 ml to values of up to 170 ml. This increase in capillary blood volume will cause them to be distended and thus the total surface area of the alveolar-capillary membrane will be increased. It is probable that it also becomes thinner. Another possible mechanism which would increase the diffusing capacity is the opening up of capillaries which are collapsed in the resting state. This is considered to be a likely occurrence but is not yet proven. The time of the transit through the pulmonary capillary has been estimated to be 0·75 sec. in the resting state. If the total cross section of the pulmonary capillaries were unaltered, then with a fivefold increase of cardiac output on severe exertion, the time of transit would fall to 0·15 sec. This increased rate of passage would not effect the total amount of oxygen diffusing into the circulating blood in unit time with increased velocity, but a fall of pulmonary venous and arterial saturation could occur if the velocity outstripped the diffusing capacity with a resultant fall of body oxygen tensions However owing to the increased capillary volume and calibre, the increased capillary velocity is not exactly proportional to the increase of cardiac output and the time of transit is thought to be of the order of 0·3–0·4 sec on maximal exertion.

Studies of the separate increases of the true diffusing capacity (alveolar-capillary membrane) and the changes of accessibility of haemoglobin to oxygen (capillary blood volume particularly) during considerable exercise show that the increase of the latter is almost twice that of the former.

Diffusing capacity and lung disease. It is only in recent years that even approximate estimations have been made of the diffusing capacity in various lung diseases. In chronic respiratory obstructive disease (asthma or bronchitis with emphysema) of any severity the diffusing capacity is reduced both at rest and on exercise In patients studied by the "two levels of oxygenation" technique, the dead space, venous admixture and diffusing capacity can all be measured simultaneously. Increased dead space and venous admixture both infer the presence of lung in which there is reduced or no gas exchange (ventilation or poorly or non-perfused alveoli; perfusion of poorly or non-ventilated alveoli) One would therefore expect the diffusing capacity (which is largely a measure of the size and nature of the effective blood-gas interface) to be reduced in proportion to the sum of the venous admixture and increased dead space. This has been found to be the case. If there is also a reduction of capillary bed throughout the whole lung then the diffusing capacity should be even lower than would be calculated by merely subtracting the fraction of diffusing capacity lost by dead space and venous admixture effects. Although present techniques are not yet accurate enough to be certain, there is a strong suggestion that the diffusing capacity is slightly less than the values obtained by this calculation

If there is variable and reversible impairment of regional lung ventilation caused by

by use of graphs and trial and error, the only mean alveolo-capillary gradient (and thus diffusing capacity) and venous admixture values that will give the appropriate alveolar-arterial gradient (membrane plus venous admixture components) at each level of oxygenation are determined. The solution in each case is unique. This is an elaborate technique requiring considerable skill and special facilities The levels of blood oxygenation have to be such as to cause considerable changes in the order of the membrane and venous admixture components of the A–A gradient. Further extreme hypoxia is to be avoided for the patient's safety and to ensure that there are not marked changes in ventilation and its distribution (venous admixture) or in the cardiac output (diffusing capacity). However, this method has been described in so far as it has greatly added to our knowledge of lung physiology and has a new and exciting future with the development of the more precise methods of blood-gas tension measurements previously mentioned

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control of blood circulation through the various parts of the lungs has not yet been discussed.

Despite an enormous amount of research this question has not yet been resolved. Investigations in both animals and humans have so far yielded many contradictory results However, the following facts are reasonably established. The pulmonary circulation has pressor receptors in great profusion, both in the arteries and veins. Afferent impulses have been demonstrated in the vagus, synchronous with pulsatile changes in the pulmonary circulation, and independent of systemic circulatory pressure changes. Under carefully controlled experimental conditions in dogs, both vasoconstrictor and vasodilator responses can be obtained by varying degrees of stimulation of both the sympathetic and vagal supply of the lungs. Acetylcholine, when injected into the pulmonary circulation in sufficiently small doses to avoid systemic responses, causes a slight fall in the pulmonary vascular resistance in both animals and humans. Ganglion-blocking agents appear to cause a fall in pulmonary vascular resistance, particularly if it is already abnormally raised by other experimental or pathological factors. This action is extremely variable and more work needs to be done. Great care is needed to prevent the experimental conditions from altering the lung mechanics, blood volume or outflow pressures, or causing secondary effects on the systemic circulation. These findings, at present, have little or no practical application in clinical medicine nor do they help our understanding of the distribution of pulmonary blood flow in health and disease.

More definite evidence is available concerning the effect of reduced oxygen tensions on the pulmonary blood distribution. If either an animal or man breathes low tensions of oxygen (10–12 per cent), then there is a definite rise in the pulmonary vascular resistance The outflow pressure of the lungs remains unaltered and it is therefore considered that there is a reduction of the calibre somewhere in the pulmonary circulation. This response appears to be quite independent of autonomic nerve supply and activity. It is generally considered to be due to vasoconstriction in the small pulmonary arteries (calibre 100–1000 μ) which contain muscle in their walls, but this is far from certain The arterioles feeding the alveolar capillaries have thin walls without muscle and the local alveolar tensions cannot therefore act directly on the small muscled pulmonary arteries. There may be a local axon reflex from alveolus to small pulmonary arteries capable of vasoconstriction, but no chemoreceptors have been demonstrated in the alveoli either functionally or morphologically. As a fall in alveolar oxygen tension must cause a similar fall of tension in the blood in the capillaries and venules downstream, it has inevitably been suggested that these structures, despite the lack of a muscle coat, may be capable of active changes in calibre which are initiated by local hypoxia. This has been investigated by a most unusual dog experiment. The circulation through the lung was reversed so that the unsaturated blood passed through the veins, was oxygenated in the alveoli and passed on to the pulmonary artery. A change from air breathing to the breathing of low oxygen tensions still caused an increase in vascular resistance This would indicate that this increase is not due to low oxygen tensions acting in the venules downstream, although an alveolar-venular axon reflex is still a remote possibility. Further if there is an alveolar-pulmonary artery axon reflex it is completely independent of the pulmonary arterial blood oxygen tensions. A local hypoxic action on the alveolar capillaries is still an important possibility. It is known that capillaries can change their calibre independently of the perfusing pressure in a most

varying degrees of airway obstruction, due to asthma or bronchitis, then the total effective blood-gas interface and diffusing capacity will fall. It will be obvious therefore that the diffusing capacity will not have a fixed value in a particular person with this disease. It is for this reason that a single measurement of the diffusing capacity does not reliably assess the permanent lung damage. Further, although the diffusing capacity is on the whole lower in those patients with the severest disease and respiratory obstruction, it is not an entirely reliable indication of the prognosis of the patient.

Patients with severe emphysema are unable to increase their diffusing capacity to any marked degree on exercise. The development of a severe degree of arterial blood desaturation on exercise is due to this limitation of diffusing capacity rather than a further decrease of distributional efficiency.

In lung fibrosis (pneumokoniosis, scarring after tuberculosis or lung suppuration) the diffusing capacity is not usually greatly impaired Unless there is added chronic respiratory obstructive disease, gas and blood distribution remain fairly efficient and the volumes of non-functioning lung are not as great as the X-ray picture suggests. The alveolar capillaries and walls are relatively normal.

Lung diseases causing loss of function of large volumes of lung (massive lung suppuration, extensive bronchiectasis or cystic disease) or resection of lobes or a whole lung would be expected to reduce the diffusing capacity in proportion to the amount of lung affected. This is not entirely true as the increased blood flow through the remaining lung increases the capillary volume, blood content and surface area, at least at rest and during moderate exercise.

There are a number of diseases in which abnormal tissues occur in the alveolar wall (sarcoidosis, scleroderma, beryllium granuloma, asbestosis, Hamman-Rich syndrome, unclassified granulomata and reticuloses). The diffusing capacity is mainly reduced because of the increased impedance to the passage of oxygen through the alveolar walls. However, many of these patients also suffer an actual reduction of blood-gas interface and of diffusing capacity due to alveolar underventilation and interference with capillary circulation (as judged by increased venous admixture and dead space). The striking correlation between the increase of dead space and venous admixture suggests, however, that many of the alveoli causing venous admixture and dead space effects are the same alveoli which are still ventilated and perfused but without any significant gas exchange The dead space is almost always more increased than the degree of venous admixture and this would suggest that capillary circulation may be more interfered with than alveolar ventilation. These patients rarely show marked arterial desaturation and cyanosis at rest, except in the terminal stages. This is due to the normal large initial alveolar-capillary oxygen tension gradient (60 mm. Hg) which is further increased by hyperventilation. As in severe emphysema the limited diffusing capacity becomes strikingly manifest on exercise when these patients become extremely cyanosed and distressed

Distribution of Blood Flow to the Lungs

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underventilated alveoli in both normal subjects and
as to whether there is any local, autonomic or central

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oxygen tensions [illegible]ting in the [illegible]
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extraordinary manner. The breathing of carbon monoxide without hypoxia causes a fall in pulmonary vascular resistance and this is thought to be due to a loss of tone caused by enzymatic poisoning in the capillary walls. It is conceivable that metabolic changes induced by hypoxia might cause an increase in capillary tone These observations and speculations serve to emphasize our very limited knowledge of pulmonary circulatory physiology.

The reduction of regional blood flow by local alveolar hypoxia has been well established in animals and humans. If a main bronchus is blocked or fed low oxygen tensions then the poor oxygenation of half the cardiac output causes a considerable fall of arterial blood saturation In animals (dogs) the arterial saturation becomes almost normal in about 10–20 min. showing a dramatic reduction of the blood flow through the hypoxic lung. In the human this effect, although present, is not so marked or consistent.

There is no doubt that *the reduction of blood flow to poorly ventilated (hypoxic) lung is advantageous providing there is adequate available oxygen and functioning lung elsewhere* However, under general hypoxic conditions or with widespread lung disease, such a mechanism may be dangerous to the organism. There is evidence that there are central mechanisms which override these local adjustments if the total organism is threatened by dangerous hypoxia. The hypoxic increase in pulmonary vascular resistance in dogs will disappear if the arterial blood saturation falls below about 55 per cent.

With regard to the effect of high carbon dioxide tension on the general or local pulmonary circulation, a number of experiments suggest that it has an action similar to but less marked than hypoxia. Results however are conflicting and the importance of carbon dioxide in this role is denied by several weighty authorities. A definite correlation between the level of arterial P_{CO_2} and the degree of pulmonary hypertension has been shown in chronic obstructive respiratory disease but these may merely be common findings late in the disease and causally unrelated

Finally, there are the effects of mechanical changes in the lung on the local circulation. If a lung or lobe collapses then the circulation falls proportionately. *This is thought to be primarily due to mechanical obstruction of the circulation rather than to the fall in local* ventilation which, however, must also play a part. In an ingenious animal experiment a lung was filled with oxygen and then blocked. Oxygen is rapidly absorbed under these conditions and *the lung collapsed completely in 5 min. The lung circulation fell pari passu* with the degree of collapse, again suggesting that the reduction of flow was mainly due to mechanical causes

There is also evidence that if the compliance of a portion of lung decreases, the local blood flow is also reduced. This may be partly due to a resultant reduction in ventilation and alveolar oxygen tension. There are, however, experimental data that there is a *collapsing effect* on the small pulmonary veins or venules under these conditions The effect of increased negative pressure across the lung is of considerable interest. If airway resistance is normal the alveolar pressures do not alter very greatly from atmospheric pressure. As negative intrathoracic pressures are transmitted immediately to the whole pulmonary circulation there must be some collapsing effect on the alveolar vessels when the endothoracic and endovascular pressures fall. In normal subjects there is a slight fall of left ventricular output and pulse pressure on inspiration. This is more marked in patients with increased negativity of intrapleural pressure. A markedly weakened pulse on

inspiration is described as *pulsus paradoxus*, a confusing term as it occurs to a lesser degree in normal subjects. *Pulsus paradoxus* (not due to pericardial constriction) is usually attributed to an increase in the capacity of the pulmonary vascular bed on inspiration. It could also be explained by a transient damming back of blood by increased alveolar vessel resistance. *Pulsus paradoxus* is very marked in conditions (asthma, acute bronchitis) where there is greatly increased airway resistance. The laboured and delayed expiration emphasizes the phenomenon. In these patients there is considerable negativity of alveolar pressure on inspiration owing to airway resistance and capillary compression is unlikely to be marked. The *pulsus paradoxus* effect may be largely due to a direct fall in aortic and arterial pressures due to the extreme negative intrathoracic pressures occurring on inspiration, rather than actual changes in stroke volume.

Finally, let us consider the changes in regional lung circulation in lung disease. It is a matter of common observation that there is a great reduction in blood flow to diseased areas of lung as the arterial saturation and venous admixture is frequently normal in patients with quite severe local disease (bronchial blockage, lobar pneumonia, bronchiectasis, local distortion or overdistension, tuberculosis, collapse) In the case of collapse this reduction may be largely mechanical and not vasomotor. In lobar pneumonia the reduction in flow may be partly related to the great decrease in compliance (see above) or increased alveolar pressure as well as local hypoxia. In infective conditions (tuberculosis, bronchiectasis with local infections), endarteritis and thrombosis must play an important part. The exact role of the local hypoxic vasoconstriction is therefore exceedingly difficult to assess under these varied conditions.

The maintenance of a large flow of blood through underventilated alveoli in chronic obstructive respiratory disease has been demonstrated and described in the previous section. It has already been suggested that there are limitations to the local correlation of ventilation and perfusion when the condition is widespread, and that central mechanisms may inhibit excessive local vasoconstriction A number of workers are now attempting to assess the magnitude of local vasoconstriction in underventilated alveoli in lung disease by eliminating it with acetylcholine infusion and studying the resultant venous admixture changes. The possible adverse effect of drugs given to combat "bronchospasm" on regional vascular adaptations to local decrease of ventilation is another interesting field of study.

Lung Blood Volumes

It has always been an attractive hypothesis that certain regions of the body circulation act as reservoirs and contain a considerable volume of blood which can be made rapidly available elsewhere in circulatory emergencies such as haemorrhage, marked changes of posture or exercise. If such reservoirs exist, then certain vessels containing considerable volumes of blood must be able to rapidly reduce their capacity under certain conditions and increase their capacity once more when the emergency is over This would demand extremely compliant vessel walls (large changes in volume with small change in endovascular pressure) or a rapid change in the compliance itself due to vasometric action. The former action is more likely in the venous system and the latter in the arterial system.

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considered that sudden demands for increased blood volumes in any part of the body are met by a decrease of both arterial and venous capacity in the parts of the general circulation not affected by the emergency. The lung circulation makes an equal but proportionately larger contribution. Owing to the very slight arterial vasometricity and small and relatively fixed capillary blood volume in the pulmonary circulation, it is considered that the smaller pulmonary veins are probably the main site of blood volume variation in the lungs.

Let us first consider the methods employed to determine the blood volumes and their changes in the lungs and chest

If a known amount of dye (or any tracer substance, *i.e.* radioactive material) is injected into the antecubital vein, the concentration of the dye can be followed in the brachial artery after the blood concerned has passed through the whole chest circulation. The mean dye concentration during the time the dye passes the sampling point gives a measure of blood flow (cardiac output) as follows:

$$\text{Flow} = \frac{\text{Amount of dye injected}}{\text{Mean dye concn.} \times \text{time to pass sampling point}}$$

The volume of blood in the vessels between injection and sampling point is determined as follows·

$$\text{Volume} = \frac{\text{Flow}}{\text{Time of circn. from injn. to sampling point}}$$

For these equations to be valid the dye must be mixed equally throughout all the blood in the system studied, and the mean circulation time must truly represent the mean velocity of all the blood in the system. The passage of the dye through a ventricle greatly helps mixing, but these assumptions are not entirely valid.

Changes in blood volume in the lung can also be determined by changes in total and functional residual capacity. If this technique is combined with trunk and limb plethysmography some measure of the shifting of blood volumes in the circulation can be obtained

The volumes of various parts of the "chest" circulation can be determined by injecting and sampling dye at many different points (right atrium, pulmonary artery, left atrium, aorta, etc.). Ventricular and atrial volumes are also measured by various stereoscopic radiological techniques using radio-opaque injections and ciné-radiography The blood volume measured from superficial arm vein to brachial artery is termed the central or thoracic blood volume It varies from 1·75 to 2·6 litres and is about one-third of the total blood volume. It is estimated that the volume of blood in the systemic venous and arterial system included in this estimation is about 0·3 litres. Of the remaining blood (1·45 to 2·3 litres) about three-quarters is in the lung circulation and one-quarter is in the heart chambers. Estimations of the mean volumes in the right and left heart by dye and radioscopic techniques yielded figures of 550 and 130 ml. respectively. A "direct" dye estimation of the volume of blood in the lungs during thoracotomy in three cases gave a mean value of 1·76 litres.

If a subject lies down then about 600 ml. of blood are shifted from the lower extremities to the upper body. Three-quarters of this blood is accommodated by the chest and it is

estimated that, again, three-quarters of the increase in thoracic blood volume is in the pulmonary circulation. No marked change in abdominal blood volume has been found. There is a fall in the pulmonary blood volume, not only on standing but also under conditions causing systemic vasodilatation (amyl nitrite, heat, spinal or general anaesthesia), after reduction of total circulating blood volume (haemorrhage) and during positive pressure breathing.

Sjöstrand has carefully surveyed the question of reservoir action during conditions demanding a new distribution of blood (shock, exercise) and considered that the effects of the thoracic "reserve" and of the reduction of the capacity of systemic beds by arterial and venoconstriction are probably about equal.

For the reasons already mentioned the thoracic "reserve" blood is thought to be mainly in the smaller veins of the lung and not the larger vessels. The accessibility of the thoracic reserve blood to the left ventricle may allow a sharp rise of ventricular output in early exercise before there is an increased return of blood to the heart. The residual ventricular blood is very small (about 20 ml.) and this could make little contribution under these conditions.

The reader is warned that the accuracy of many of these volume determinations is still in doubt and that the figures given are very approximate and are only to provide the reader with some idea of the probable order of the volumes concerned.

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CHAPTER 4

THE NATURE OF PULMONARY HYPERTENSION

BY JOHN GOODWIN

THE term pulmonary hypertension is commonly used to denote arterial hypertension, but the importance of pulmonary venous hypertension must not be forgotten, and there is much to be said for qualifying pulmonary hypertension with the appropriate adjective, arterial or venous.

As has been pointed out in Chapter 2, the study of the physiology of the pulmonary circulation bristles with difficulties and differences of opinion Enormous gaps still exist in the knowledge of basic mechanisms, and physiological measurements are difficult and capricious.

Nevertheless, from the clinical standpoint much has been learned about the pulmonary circulation in recent years, and while some assumptions are inevitable, the results of clinical experience based upon haemodynamic study permit a logical assessment of the clinical disorders which affect the pulmonary circulation.

Pulmonary Arterial Hypertension

By definition, this exists when the pulmonary artery pressure exceeds the maximum normal limit, defined by Wood (1956) as 30/15 mm. Hg, measured from the sternal angle, the maximum normal mean pressure being 22 mm Hg

The principal factors which maintain pulmonary arterial pressure are the output of the right ventricle, which determines the pulmonary flow, and the resistance to flow offered by the pulmonary vascular bed. Other factors are certainly concerned also, such as pulmonary blood volume, respiratory movements, and elasticity and inflation of the lungs. Pulmonary arterial hypertension can occur when either or both the pulmonary flow and the vascular resistance is increased, and may be classified as follows:

1. *Hyperdynamic* { Increased pulmonary flow / Low pulmonary resistance
2. *Obstructive* { Increased pulmonary resistance / Low pulmonary flow
    a. Passive.
    b. Vasoconstrictive.
    c. Obliterative

This classification is modified from that of Wood (1956). Fig. 15 shows the sites of obstruction and the possible causes.

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Obstructive pulmonary hypertension

In its widest sense this term denotes hypertension resulting from a lesion which increases resistance to flow and hinders blood from entering or leaving the pulmonary vascular bed. It includes lesions of the left ventricle, left atrium, and pulmonary veins, capillaries and arterioles The pulmonary vascular resistance is thus elevated.

A. **Passive pulmonary hypertension** occurs when elevated pressures in the left side of the heart are transmitted to the pulmonary artery, and therefore results from antecedent pulmonary venous or postcapillary hypertension arising distal to the pulmonary capillary bed It occurs in mitral stenosis, in tumours of the left atrium, and in left ventricular failure, and will be discussed further under pulmonary venous hypertension.

B. **Vasoconstrictive pulmonary hypertension** denotes arterial hypertension due to constriction of the arterioles from any cause. Good evidence that acute vasoconstriction can occur was obtained by Gorlin *et al.* (1958), who noted a rise in pulmonary artery pressure and fall in output in a patient with idiopathic pulmonary hypertension in whom a stellate block was being attempted. It is now believed that there are a number of precipitating factors, notably certain drugs, alterations in oxygen tension of the pulmonary arterial blood, antecedent pulmonary venous hypertension, and prolonged and excessive pulmonary blood flow in certain cases of congenital heart disease. It is probable also that pulmonary arterial hypertension itself tends to provoke vasoconstriction, leading to a vicious circle ("Reactive Hypertension", Wood (1956)). The syndrome of primary or idiopathic pulmonary hypertension may be an example of vasoconstriction from unknown cause, but is perhaps better considered in the group of obliterative hypertension.

1 *Hypoxia* The recent studies of Harris *et al* (1956), have confirmed the generally accepted view that hypoxia can cause pulmonary vasoconstriction (Chapter 2). In patients with cor pulmonale the right ventricular systolic pressure varies inversely with the arterial oxygen saturation, the former reaching high levels No relation between cardiac index and right ventricular systolic pressure has been found, which would be expected if hypertension were due to increased output (Mounsey *et al.*, 1952). The way in which hypoxia causes vasoconstriction is uncertain, but a direct effect upon the arterioles of low oxygen tension in the pulmonary arterial blood is thought probable, although a reflex mechanism has been postulated, and the effects of hypoxia can certainly be very complex (Aviado *et al.*, 1957) (Chapter 2) Results of the effect of sympathetic denervation of the lung on vasoconstriction induced by hypoxia are conflicting, and the matter remains undecided. Cournand (1957) has shown that eight to ten per cent oxygen given to one lung caused no alteration in the partition of blood flow between the two lungs and no rise in pulmonary arterial pressure. But when 12 per cent oxygen was given to both lungs, a considerable rise in pressure occurred, which led him to postulate the presence of a local reflex producing vasoconstriction and actuated by the low oxygen tension in the alveolar gases. Whatever the mechanism of hypoxic vasoconstriction, its practical applications are of the greatest importance It explains why pulmonary heart failure can be precipitated so easily by lung infections which impair ventilation and respiratory exchange, and why oxygen is so important in treatment.

To regard pulmonary hypertension in chronic respiratory disease as merely the result of vasoconstriction and increase in output would be to oversimplify a complicated problem. Many factors such as unequal ventilation of different parts of the lung, shunting of

Hyperdynamic pulmonary hypertension

This occurs where the pulmonary blood flow is greatly increased past the limit of elasticity of the pulmonary vascular bed. It will be recalled that the normal pulmonary vascular resistance is very low, and a considerable increase in flow, probably up to three times the resting cardiac output, can be accommodated in the distensible and elastic pulmonary vessels without a rise in pressure. For example, on exercise in the normal person the pulmonary blood flow rises, and the resistance falls as the vessels dilate, and therefore the pressure does not significantly increase. Brofman *et al.* (1957), have shown that when the pulmonary artery is completely occluded the total circulation can be accommodated in the other lung with a decrease in pulmonary vascular resistance But when the limit of elasticity is reached, a linear relationship between pressure and flow

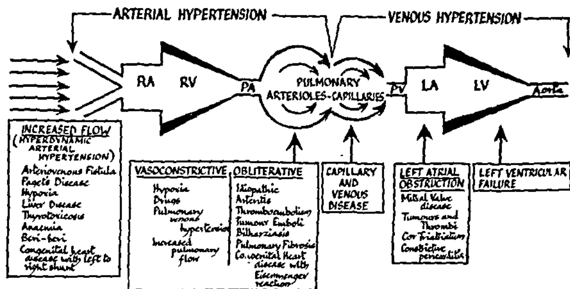


FIG 15 Diagram showing the possible sites of obstruction to pulmonary blood flow, and the disorders which may be involved.

appears, the system acting as a series of rigid tubes, each increment of flow adding a similar increment of pressure. Generally, very large flows, greater than 15 litres/min. are necessary before the pressure rises. Such circumstances may be met in severe anaemia, multiple arteriovenous fistulae, Paget's disease of bone, hyperthyroidism, cor pulmonale, hepatic disease, and vitamin B deficiency

Most of these conditions have *in common an increased plasma volume, high cardiac* output and vasodilatation The pulmonary blood vessels are normal, but in some cases such as cor pulmonale, an element of obstructive hypertension may be added, so that very high levels of pulmonary artery pressure may be attained.

The pulmonary blood flow is increased in congenital heart disease with left to right shunt. The small pulmonary blood vessels are often normally distensible and any hypertension therefore solely hyperdynamic. But in many cases vasoconstrictive and obliterative changes exist and aggravate the hypertension. These will be fully discussed in Chapter 9.

Obstructive pulmonary hypertension

In its widest sense this term denotes hypertension resulting from a lesion which increases resistance to flow and hinders blood from entering or leaving the pulmonary vascular bed It includes lesions of the left ventricle, left atrium, and pulmonary veins, capillaries and arterioles The pulmonary vascular resistance is thus elevated.

A. **Passive pulmonary hypertension** occurs when elevated pressures in the left side of the heart are transmitted to the pulmonary artery, and therefore results from antecedent pulmonary venous or postcapillary hypertension arising distal to the pulmonary capillary bed. It occurs in mitral stenosis, in tumours of the left atrium, and in left ventricular failure, and will be discussed further under pulmonary venous hypertension

B. **Vasoconstrictive pulmonary hypertension** denotes arterial hypertension due to constriction of the arterioles from any cause. Good evidence that acute vasoconstriction can occur was obtained by Gorlin *et al.* (1958), who noted a rise in pulmonary artery pressure and fall in output in a patient with idiopathic pulmonary hypertension in whom a stellate block was being attempted It is now believed that there are a number of precipitating factors, notably certain drugs, alterations in oxygen tension of the pulmonary arterial blood, antecedent pulmonary venous hypertension, and prolonged and excessive pulmonary blood flow in certain cases of congenital heart disease. It is probable also that pulmonary arterial hypertension itself tends to provoke vasoconstriction, leading to a vicious circle ("Reactive Hypertension", Wood (1956)) The syndrome of primary or idiopathic pulmonary hypertension may be an example of vasoconstriction from unknown cause, but is perhaps better considered in the group of obliterative hypertension

1 *Hypoxia* The recent studies of Harris *et al* (1956), have confirmed the generally accepted view that hypoxia can cause pulmonary vasoconstriction (Chapter 2). In patients with cor pulmonale the right ventricular systolic pressure varies inversely with the arterial oxygen saturation, the former reaching high levels. No relation between cardiac index and right ventricular systolic pressure has been found, which would be expected if hypertension were due to increased output (Mounsey *et al*, 1952) The way in which hypoxia causes vasoconstriction is uncertain, but a direct effect upon the arterioles of low oxygen tension in the pulmonary arterial blood is thought probable, although a reflex mechanism has been postulated, and the effects of hypoxia can certainly be very complex (Aviado *et al*, 1957) (Chapter 2) Results of the effect of sympathetic denervation of the lung on vasoconstriction induced by hypoxia are conflicting, and the matter remains undecided Cournand (1957) has shown that eight to ten per cent oxygen given to one lung caused no alteration in the partition of blood flow between the two lungs and no rise in pulmonary arterial pressure But when 12 per cent oxygen was given to both lungs, a considerable rise in pressure occurred, which led him to postulate the presence of a local reflex producing vasoconstriction and actuated by the low oxygen tension in the alveolar gases. Whatever the mechanism of hypoxic vasoconstriction, its practical applications are of the greatest importance. It explains why pulmonary heart failure can be precipitated so easily by lung infections which impair ventilation and respiratory exchange, and why oxygen is so important in treatment.

To regard pulmonary hypertension in chronic respiratory disease as merely the result of vasoconstriction and increase in output would be to oversimplify a complicated problem. Many factors such as unequal ventilation of different parts of the lung, shunting of

Hyperdynamic pulmonary hypertension

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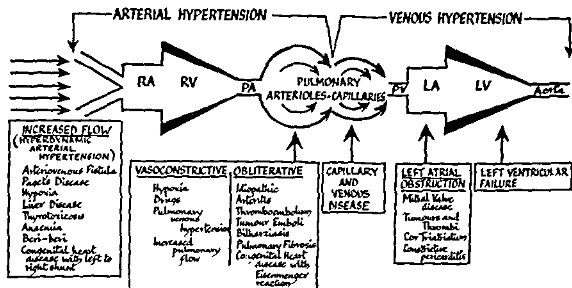


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of these drugs in an acute observation, but, as with drugs purporting to produce pulmonary vasoconstriction, the way in which they act is confusing. Unless other effects, such as heart rate, cardiac output and systemic blood pressure are rigidly controlled, false deductions can be made. Further difficulties arise when the drug used has more than one effect, such as adrenolytic, sympatholytic and local actions.

Reduction of pulmonary arterial pressure may be achieved in various ways—by a reduction in cardiac output (by pooling of blood in the systemic vascular bed, decrease of venous return, and reduced right ventricular stroke output); in certain circumstances by a reduction in systemic blood pressure, and by pulmonary vasodilatation When the cardiac output falls, then the accompanying fall in pulmonary arterial pressure must be

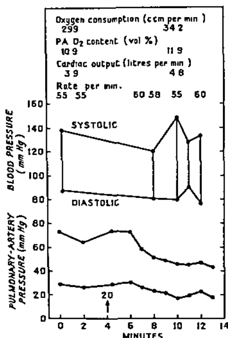


Fig 16 The haemodynamic effects of hexamethonium in mitral stenosis The figure 20 above the arrow at 4 min denotes the dose of hexamethonium in mgm injected through the cardiac catheter placed in the pulmonary artery.

The pulmonary artery pressure falls, the cardiac output increases, and the heart rate is not significantly altered There is a slight fall in systemic blood pressure, followed by a transitory rise, at the time of maximum fall in pulmonary artery pressure

regarded as passive, and secondary to this It follows that unless cardiac output is measured concurrently with pulmonary arterial pressure, no deductions whatever can be made as to the mechanism of pulmonary hypotension, should it occur. This difficulty is well illustrated by the effects of ganglion blocking agents, especially hexamethonium, which often lowers pulmonary arterial pressure, but which also frequently reduces systemic blood pressure and cardiac output The output has also been shown to fall without significant reduction in systemic pressure. However, in a minority of subjects, pulmonary artery pressure falls while cardiac output rises, without change in heart rate (Goodwin *et al.*, 1958) (Fig 16). This finding provides strong presumptive, though not certain, evidence of active pulmonary vasodilatation, since the subjects studied had no evidence of impaired left ventricular function and were not in left ventricular failure Pulmonary hypertension due to left ventricular failure also may be reduced by hexamethonium, with consequent rise in cardiac output. The mechanism is probably release of systemic peripheral vasoconstriction, fall in systemic blood pressure, increase in left ventricular stroke volume,

pulmonary arterial blood through non-aerated areas of lung, uneven mixing of blood and gases, diffusion block across the alveolo-capillary membrane, air trapping, carbon dioxide retention, impaired bellows function of the lungs, impaired ventilation due to chest deformity, poor chest movement, and organic disease of the vessels may all play a part. McIlroy and Apthorp (1958) studied pulmonary function in patients with pulmonary hypertension, but found no direct relationship between the two, although patients with hypertension in general showed impairment of lung compliance and diffusing capacity. Perhaps the postulate that hypoxia is the final common path is explanation enough, but insufficient is known at the present time to be dogmatic on this point. These matters will be discussed more fully in Chapters 11 and 12.

2 *Pharmacology*. The effect of drugs on the pulmonary circulation has already been discussed in Chapter 2, but it is worth considering here the part which they may play in producing, maintaining, or releasing pulmonary arteriolar vasoconstriction in pulmonary hypertension Pressor drugs such as nor-adrenaline and phenylephrine have been said to produce vasoconstriction in the pulmonary bed (Daley, 1957), but their effect on the pulmonary circulation is not necessarily always the same as on the systemic, in which the normal resistance is eight times higher, owing to greater normal intrinsic tone in the systemic arterioles. Histamine, a systemic vasodilator, is believed to constrict the pulmonary vessels, while the dihydrogenated alkaloids of ergot, which lower systemic peripheral resistance by virtue of their adrenolytic and sympatholytic effects, have a direct pulmonary vasoconstrictor action. The matter is complicated further because drugs may augment pulmonary artery pressure by increasing cardiac output or pulmonary venous pressure, in addition to, or independent of, arteriolar vasoconstriction Thus nor-adrenaline has been said sometimes to raise pulmonary arterial pressure passively by raising pulmonary venous pressure initially, while 1-hydrazinophthalazine raises pulmonary arterial pressure by increasing heart rate and cardiac output

The effect of drugs in producing or increasing pulmonary hypertension to a dangerous degree clinically is not thought to be great with the exception of Serotonin (Chapters 2 and 12), although 1-hydrazinophthalazine has potentially dangerous effects when severe obstruction exists in the left side of the heart, as in mitral stenosis (Aitchison *et al.*, 1955). It might be expected that pressor drugs such as ephedrine, adrenaline and isopropylnoradrenaline which are so frequently used to relieve wheezing, might cause pulmonary vasoconstriction, which would be disadvantageous in mitral stenosis Personal experience with isopropylnoradrenaline given by inhalation during cardiac catheterization in patients with mitral stenosis has not revealed any significant rise in pulmonary artery pressure. Tachycardia and changes in cardiac output have been minimal This indicates that, when given by inhalation, no untoward pulmonary hypertensive effect is likely to occur. However, a marked tachycardia, which might be induced in sensitive subjects, would increase output and pressure and would be undesirable Alexander *et al.* (1958) did not find any change in the pulmonary vascular resistance in the majority of their patients after inhalation of adrenaline.

with mitral valve disease. In animals with normal pulmonary vasculature acute observations suggest that a rise in left atrial pressure can passively distend the pulmonary vessels and increase blood flow (Chapter 8).

4. *Excessive pulmonary arterial pressure and flow.* Massive pulmonary blood flow due to a left to right shunt in congenital heart disease frequently causes hyperdynamic hypertension, but in many cases the pulmonary vascular resistance is also raised, and this elevation is thought to be due to arteriolar vasoconstriction resulting from the increased flow and pressure. Increased flow alone does not necessarily cause vasoconstriction, for a normal pulmonary pressure and resistance may be found after many years of excessive pulmonary blood flow in some cases of atrial septal defect and of patent ductus arteriosus (Chapter 9) It is possible that conditions other than congenital heart disease which cause high right ventricular output and pulmonary flow may act in the same way, but evidence is lacking The problems of vasoconstrictive pulmonary hypertension in congenital heart disease will be considered in detail in Chapter 9.

C. Obliterative pulmonary hypertension. This group comprises patients whose pulmonary vascular bed has become obliterated by disease, and includes thrombo-embolism, bilharzial disease, specific forms of arteritis (such as polyarteritis nodosa), strangulation of the vascular bed by pulmonary fibrosis and emphysema, and many cases of "primary" or idiopathic pulmonary hypertension, and of congenital heart disease with right to left shunt (Eisenmenger Reaction) (Chapter 9). It is likely that the majority of cases of obliterative hypertension are due to thrombo-embolism, specific forms of arteritis being rare.

The elevated pulmonary arteriolar resistance of organic arteriolar obstruction is not accompanied by pulmonary venous hypertension But in certain types of congenital heart disease progressive restriction of the pulmonary vascular bed follows vasoconstriction (Chapter 9).

In obliterative hypertension the pulmonary resistance cannot be reduced by any means, except perhaps recanalization of thrombosed arterioles, and organic occlusive disease can be demonstrated at autopsy. It is thus that the most sinister and intractable forms of pulmonary hypertension are found in this group

The contribution of bronchial-pulmonary artery anastomoses to pulmonary hypertension is uncertain Such communications are best seen in patients with pulmonary atresia, when measurement of pulmonary artery pressure is not possible (Chapters 1 and 9).

The Important Distinction between Venous and Arterial Hypertension

Accurate clinical assessment of pulmonary hypertension requires a clear understanding of the difference between the two major sites for obstructive pulmonary hypertension The term "pulmonary hypertension" is now too loose and should always be qualified by the adjective venous or arterial. Absence of evidence of venous hypertension localizes the site of the pulmonary vascular disorder to the arteriolar bed, and should exclude lesions distal to it It must be remembered, however, that since preceding venous hypertension is one of the common causes of arteriolar vasoconstriction, both venous and arterial hypertension of necessity often co-exist, as in mitral stenosis.

reduction in left ventricular filling pressure and pulmonary venous pressure, and hence reduction in pulmonary arterial pressure. The action of digitalis on lowering pulmonary arterial pressure in left ventricular failure may be ascribed to increased left ventricular stroke volume with a resultant rise in output This "passive" reduction in pulmonary hypertension is said to be accompanied by a reduction in pulmonary blood volume due to a shift of blood to the systemic vascular bed. Direct "active" pulmonary vasodilatation *may perhaps occur in these circumstances*, but definite evidence of this is lacking Sarnoff *et al.* (1953) have shown in animals that the pulmonary vascular bed behaves passively, its volume depending principally upon the volume of the systemic vascular bed, systemic vasoconstriction causing a rise in pulmonary blood volume and in pulmonary vascular pressures, while systemic vasodilatation has the reverse effect.

Good evidence of direct pulmonary arteriolar vasodilatation due to drugs is provided *by the work of Cournand and his colleagues (Harris et al., 1956), and Wood et al. (1957)*, with acetylcholine The former showed in normal man that infusion of acetylcholine into the pulmonary artery at a rate of 0·5 mgm. per min caused a slight fall in pulmonary artery pressure, which was much greater when the pressure had been previously increased by hypoxia, even when the hypoxia was maintained. This fall was not secondary to reduction in pulmonary venous pressure The cardiac output, which had been increased by the hypoxia, remained unchanged, or increased still further The *implication, therefore,* is that acetylcholine produced vasodilatation in the lungs, the site being uncertain Wood and his colleagues, studying patients with mitral stenosis showed that acetylcholine produced a fall in pulmonary arterial pressure, with a rise in pulmonary venous pressure. Changes in systemic blood pressure were slight and usually in the direction of a rise The cardiac output when measured showed a rise, no change, or a negligible fall. The association of a rise in pulmonary venous pressure with a fall in pulmonary arterial pressure offers strong evidence for direct active arteriolar dilatation Furthermore, these results support the concept of obstructive pulmonary arterial hypertension due to vasoconstriction, and it is of interest that the fall of pressure was no greater when the initial pressure was greatly elevated than when it was only moderately so, indicating the presence of vasoconstriction of varying degrees of severity

3 *Pulmonary venous hypertension.* A raised pulmonary venous pressure is transmitted back to the pulmonary artery, producing passive pulmonary hypertension, for the mean pulmonary artery pressure must be at least 10 mm Hg higher than the mean pulmonary venous pressure in order to preserve the normal gradient Thus a mean left atrial (pulmonary venous) pressure of 20–30 mm Hg necessitates a mean pulmonary arterial pressure of 30–40 mm. Hg, which is above the normal maximum of 22 mm Hg (Wood, 1956) Antecedent venous hypertension is now considered to precipitate arteriolar constriction, *which produces an elevated arteriolar resistance* Mitral stenosis is by far the commonest cause of sustained left atrial and pulmonary venous hypertension, rarer causes being left atrial tumours, cor triatriatum, and stenosis of the pulmonary veins. Left ventricular failure is the most frequent cause of less sustained left atrial hypertension Evidence obtained from studies in mitral valve disease and from other sources suggests that the pulmonary veins are capable of active contraction and dilatation and are not mere passive tubes. The evidence for pulmonary venous hypertension causing arteriolar vasoconstriction has been mainly obtained from haemodynamic and angiographic studies in patients

present. Wade *et al.* (1956), however, found in mitral stenosis that the pulmonary arterial pressure never fell without a preceding fall in left atrial pressure. This harmonizes well with the concept of pulmonary arteriolar vasoconstriction being due to pulmonary venous hypertension, but leaves undecided the exact mechanism of its production. These workers postulated a local reflex, uninfluenced by the autonomic nervous system. They cast further doubt on the participation of the autonomic nervous system in the control of the pulmonary vasculature when they failed to produce any fall in pulmonary vascular resistance, whatever the initial level, with the adrenergic blocking agent hydergin (MacKinnon *et al.*, 1956).

Evidence for significant neurogenic control of the lung vessels in man is scanty, but cannot be neglected. Experiments on perfused lungs of animals, usually dogs, have been beautifully executed and carefully controlled by de Burgh Daly and his colleagues, and well summarized in the Symposium on Pulmonary Circulation and Respiratory Function in Dundee in 1956 (Daly, 1956). These experiments showed that both vasoconstrictor and dilator fibres were present in the autonomic nerve supply of the lungs, and that most of the constrictor fibres were sympathetic in origin with cell stations in the stellate and middle cervical ganglia, but with adrenergic postganglionic neurones. Accepting these facts, it becomes necessary to know the site of action of the vasomotor nerve fibres, and whether they have any appreciable functional significance in man in health and disease.

The site of action is still debatable. Daly (1956) states that vascular nerve impulses may cause an intermittent and asynchronous constriction of pulmonary arterioles supplying individual parts of the lung, thus determining the number of localization of perfused units. *Intermittent activity of alveolar capillaries and lobar bronchi has been postulated*, as has constriction of venules, which might serve as a control mechanism for passively dilating alveolar capillaries. If, as Daly suspected, some of the capillaries were constricted in his lung perfusion experiments, then this would harmonize with the hypothesis that stimulation of sympathetic nerves closes down pulmonary artery—pulmonary vein communicating channels or the larger alveolar capillaries, causing a diminution of total lung flow or shunting of blood through a higher vascular resistance area of inactive or partially constricted capillaries. Furthermore, Dawes (1958) has claimed the presence of both pressure and volume receptors in the left atrium which might be concerned with arteriolar constriction following pulmonary venous and left atrial hypertension Eliakim *et al.* (1958) have recently also suggested that receptors are present at the junction of the left atrium with the pulmonary vein, for they noted a rise in pulmonary venous, arterial, right ventricular, and right atrial pressures, with no change or a fall in left atrial pressure and in systemic blood pressure after intravenous infusion of 20 per cent saline in anaesthetized dogs. Semler *et al* (1959) have failed to confirm this work, and have suggested that the pressor effect of hypertonic saline is due to reversible agglutination of red cells in the capillaries.

Evidence in favour of neurogenic vasoconstriction in pulmonary hypertension in man has been obtained to a limited extent from acute studies with drugs Thus Gilmore *et al.* (1952) showed that hexamethonium prevented the reduction in pulmonary vascular capacity due to vasoconstriction which normally occurs on assuming the upright position, and deduced from this that the pulmonary vessels must have a neurogenic vasoconstrictor mechanism, for hexamethonium has no local vasodilator action in the doses used. Davies

The Role of the Nervous System in Pulmonary Hypertension

Studies with acetylcholine and hypoxia have shown that the pulmonary vessels have the power to constrict and dilate actively. Whether or not this is achieved entirely independently of the autonomic nervous system is a matter of controversy. The pulmonary blood vessels are known to be supplied by vasoconstrictor fibres through the sympathetic nerves, the cell stations lying in the stellate and middle cervical ganglia. The postganglionic vasoconstrictor fibres are adrenergic, while there is some evidence that dilator fibres also supply these vessels, even though the nerve endings to the pulmonary vessels are few and hard to find It might be expected that the autonomic nervous system would play a prominent part in pulmonary vasoconstriction, and might control the normal reactions whereby vascular resistance varies with pulmonary blood flow and inflow pressure. However, the evidence is far from clear cut Cournand (Harris *et al*, 1956) has suggested that hypoxic vasoconstriction in man occurs independently of the sympathetic nervous system, for it is not abolished by sympathectomy.

Daley (1957), using dogs, found a direct correlation between the rise in pulmonary artery pressure and fall in oxygen saturation of mixed venous blood, and believed the vasoconstriction to be due to the direct effect of hypoxia rather than to a reflex mechanism.

Pulmonary hypertension was induced by causing experimental pulmonary embolism in dogs with lycopodium spores by Daley (1957) and was uninfluenced by vagotomy and anterior rhizotomy Furthermore, dogs on which a sympathectomy had previously been performed showed a rise of pressure from 24/12 to 50/12 mm Hg after injection of the spores, and their response did not differ from that in the animal with an intact autonomic nervous system. If these results can be applied to man, then the evidence would suggest that embolic obstruction of the vascular bed is also uninfluenced by neurogenic mechanisms

Lee *et al.* (1954) studied the systemic arterial, net right atrial, pulmonary arterial, and pulmonary capillary pressures simultaneously in ten normal subjects performing the Valsalva manœuvre. They found a marked rise in net pulmonary arterial pressure, equivalent to the rise in net right atrial pressure and pulmonary capillary pressure. The rise in net pulmonary arterial pressure was not abolished by the previous injection of a ganglion blocking agent, tetraethylammonium chloride, as was the rise in systemic pressure, and it was concluded that there was no evidence of neurogenic pulmonary vasoconstriction These results conflicted with those of Greene and Bunnell (1950), who were able to abolish the "overshoot" in pulmonary arterial pressure with the same drug.

Other studies with ganglion blocking agents have also produced conflicting results and conclusions, due mainly to the confusion produced by effects on both the systemic and pulmonary circulations Thus Sarnoff and Sarnoff (1952) believe that the fall in pulmonary artery pressure produced by these drugs is merely secondary to systemic vasodilatation and displacement of blood from the lungs to the greater circulation.

Storstein and Tveten (1954), in clinical studies on patients with various types of pulmonary hypertension, found that the fall in pulmonary artery and capillary pressures was of the same magnitude and order, and considered that the former was a passive consequence of the latter. This must be partly the case in patients with left ventricular insufficiency, but may not be so when mitral stenosis with normal left ventricular function is

of diametrically opposed results from similar experiments by different workers, and of collateral evidence obtained by a variety of different indirect observations. Clearly no dogmatic statement can be made with our present deficient knowledge of the pulmonary circulation, a circulation which is unique in its property of accommodating a very large blood flow at low resistance. From this it follows that the normal pulmonary vessels can have little intrinsic tone. Few would argue that under experimental conditions in animals the lung vessels have been shown to have a vasomotor innervation. It may well be that under conditions of health, the neurogenic mechanism plays no part in pulmonary vasoconstriction, and this would explain the negative results of Lee and his colleagues with the Valsalva manœuvre in healthy persons. However, when the pulmonary circulation is diseased and pulmonary resistance elevated, then neurogenic influences may well be called into play, and enough evidence has been quoted to suggest that this is likely in mitral disease in which pulmonary venous hypertension stimulates reflex constriction of the arteriolar bed. The failure of nerve section to prevent the pulmonary hypertension of experimental pulmonary embolism is probably not a valid reason for discounting nervous control, since the increased pulmonary resistance in this situation is presumably the result of obliteration of the vascular bed, in which case sufficient vasodilatation to produce a fall in pressure might not be possible It would be injudicious to speculate further on the clinical importance of neurogenic control of the pulmonary circulation. Many factors are likely to be responsible for pulmonary hypertension, as has already been shown, and future research may allocate to the nervous system a place of only minor importance.

At the present time the weight of informed opinion inclines away from significant neurogenic control. Time alone will show whether this attitude is correct.

Clinical Features of Pulmonary Hypertension

Pulmonary arterial hypertension

Hyperdynamic hypertension. When hypertension is due to high pulmonary blood flow from increased cardiac output the patient may have few symptoms (other than some dyspnoea on exertion) apart from those due to the condition which has produced the high rate of flow Clinical examination reveals all the stigmata of the hyperdynamic circulation: full volume, quick rising and bounding arterial pulse; raised jugular venous pressure with normally balanced "a" and "v" waves; and warm moist vasodilated extremities. The cardiac impulse is also hyperdynamic, and the heart may be enlarged. Pulmonary and aortic ejection murmurs are audible, and the second heart sound is accentuated due to augmentation of the pulmonary component, and narrowly split, the split increasing normally on inspiration. Fig 17a shows the venous pulse in a patient with thyrotoxic heart failure, and Fig. 17b the pulmonary ejection murmur and the accentuated pulmonary valve closure in the same patient. Other physical signs will depend upon the underlying disease

When the increased pulmonary blood flow is due to a left-to-right shunt in congenital heart disease, the signs of a high cardiac output are absent, for the left ventricular output is normal or reduced. The special signs in such cases will be described in full in Chapter 9.

Following resolution of the disorder causing the high cardiac output, the signs of increased pulmonary flow and pressure subside as the pulmonary artery pressure returns

et al (1954) studying patients with mitral stenosis, noted a marked fall in pulmonary artery pressure, with no change or a rise in cardiac output after hexamethonium. These changes were unaccompanied by significant alterations in systemic blood pressure or heart rate, and these workers concluded that active pulmonary vasodilation had occurred and that this was due to release of neurogenically maintained vasomotor tone. Their results, however, did not exclude the possibility of a small shift of blood from a rigid pulmonary vascular bed into the systemic bed causing a fall in pulmonary artery pressure, but insufficient to effect cardiac output or systemic pressure. The counter argument that displacement of small amounts of blood from the lungs would not be expected to produce a profound fall in pulmonary arterial pressure might be applied to this suggestion. Support for Davies and his colleagues came from Balchum *et al.* (1957) who showed a greater decrease in pulmonary arteriolar than in total pulmonary or total peripheral resistances after methonium in patients with mitral stenosis, which suggested release of pulmonary arteriolar constriction. They also considered that shifting of blood from the lesser to the greater circulation was a factor in lowering pulmonary arteriolar resistance. However, it must be remembered that calculations of resistances, which are dependent entirely upon measurements of flow and pressure, may be fallacious in these circumstances, as shown by Goodwin *et al.* (1958), who noted that if the cardiac output fell more than the pulmonary artery pressure after methonium, the calculated resistance actually rose. This result was not, of course, due to vasoconstriction. These workers, however, reported a number of cases in which the output rose and the pulmonary artery pressure fell, in the absence of significant changes in systemic blood pressure or heart rate (Fig. 16), and reiterated the views of Davies *et al.* (1954) in favour of active vasodilatation by methonium They surveyed the reported cases of mitral stenosis investigated with ganglion blocking agents, adding thirty-two of their own, and pointed out that the effects of methonium were variable and difficult to control and interpret in view of the systemic effects produced. The effect on cardiac output was especially variable, about one-third of the total cases showing a fall, a rise, or no change respectively. They quoted three cases from the literature in which the fall in pulmonary artery pressure was accompanied by a rise in cardiac output and pulmonary venous pressure This response is similar to that obtained with acetylcholine, and strongly suggests inhibition of vasoconstrictor arteriolar tone, which must be neurogenically maintained if released by a ganglion blocking agent. The usual response, however, in mitral stenosis, was a fall in pulmonary venous pressure, accompanying a fall in arterial pressure, and favouring the concept of arteriolar constriction initiated by venous hypertension. It is possible that methonium may block arteriolar vasoconstrictor impulses stimulated by receptors in the left atrium or pulmonary veins which are sensitive to increased pressure. This will be further discussed in Chapter 8.

As has already been mentioned, Cournand and his colleagues, and Daley, found that sympathectomy had no effect on the pulmonary hyp [illegible] embolism respectively. Contradictory evidence has b [illegible] who reported clinical improvement after stellate bl [illegible] Furthermore, Aviado *et al.* (1957), working with dogs, claimed that pulmonary vasoconstriction produced by hypoxia was dependent upon intact perivascular nerve fibres and thoracic sympathetic nerves

It will be seen from the foregoing that the evidence is indeed conflicting, both in respect

to normal. Humerfelt *et al.* (1958) have shown that the raised pulmonary arterial pressure and flow in thyrotoxicosis fall when the patient becomes euthyroid.

Obstructive hypertension. When the pulmonary vascular resistance is raised, the cardiac output tends to fall, and in extreme cases the output is below normal, and tends to be fixed. This produces a totally different clinical picture to that of hyperdynamic pulmonary hypertension. In the very severe case the symptoms are characteristic, and are best illustrated by the condition of idiopathic pulmonary hypertension, in which primary heart disease is absent. The patient complains of extreme fatigue, especially on exertion; dyspnoea is usually present. Loss or disturbance of consciousness, especially on or after exertion, occurs, and is referable to the inability of the cardiac output to rise to meet the demands of exercise; skeletal muscle vasodilatation occurs, the cardiac output falls, and cerebral ischaemia results, sometimes to the extent of epileptiform seizures For the same

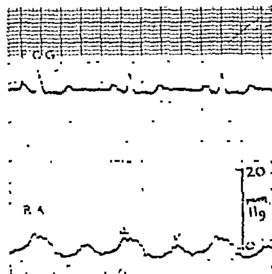


Fig 18a Right atrial pulse (R A) in idiopathic pulmonary hypertension The atrial systolic "a" wave exceeds the filling pressure "v" wave

reasons, true anginal pain due to myocardial ischaemia may be precipitated by exercise even though the coronary arteries are themselves structurally normal.

The physical signs are characteristic. The patient may be somewhat underweight, with an anxious mien, and high colour over the malar regions The extremities are cold and pale, and may be slightly cyanosed. Clubbing, and cyanosis of the tongue and the inside of the lips are absent unless there is a right-to-left shunt present. The arterial pulse is small while the jugular venous pulse shows the characteristic tall, "a" wave, which often has a characteristic "flicking" quality, and can be easily made out preceding the carotid artery pulsation The "a" wave is due to right atrial hypertrophy and hypertension and is most prominent when the atrial and ventricular septa are closed, as in mitral valve disease, cor pulmonale, and idiopathic pulmonary hypertension. The mean venous pressure is not usually raised, unless heart failure is present, and the "a" wave therefore dominates the "v" (Fig 18a). The normal "x" descent may disappear if tricuspid incompetence occurs as a result of extreme right ventricular hypertension



FIG 17a. Jugular phlebogram in thyrotoxic heart failure Both the right atrial contraction wave "a" and the filling wave, "v" are prominent, and the x and y descents are normal (PHLEB = jugular phlebogram)



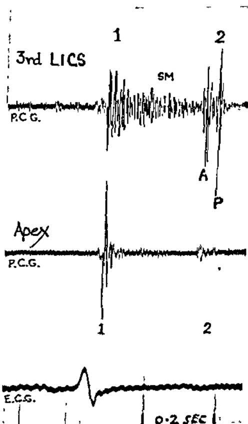


FIG 17b Phonocardiogram in thyrotoxic heart failure The pulmonary flow murmur in systole (SM) is well seen, and the pulmonary valve closure sound (2 P) is accentuated (L I C S = left intercostal space, Apex = cardiac apical impulse, A = aortic valve closure)

The Prognosis of Pulmonary Hypertension

This depends mainly upon the underlying disease, and the state of the pulmonary vascular bed. When hypertension is due solely to flow and vasoconstriction, the pulmonary artery pressure may fall to normal levels when a left-to-right shunt has been removed, as

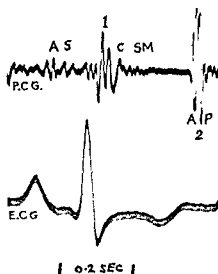
FIG [illegible]

gradient is much reduced $\frac{RVP}{LVP}$ = Right ventricular pressure as percentage of left ventricular pressure (Ventricular septal defect closed by Mr W P. Cleland at Hammersmith Hospital during total cardio-pulmonary bypass with the Melrose-N E P. pump-oxygenator)

in closure of a septal defect Reduction of pulmonary artery and right ventricular pressures after closure of ventricular septal defect and infundibular resection is illustrated by a child of five years with a pulmonary blood flow twice the systemic flow (Fig 19). The fall in pulmonary pressure after relief of diseases causing a high cardiac output, such

The cardiac impulse is right ventricular in type, shown by a tapping or lifting pulsation to the left of the lower end of the sternum and in the epigastrum. The normal localized left ventricular thrust is usually absent, and the diffuse right ventricular impulse may make the heart appear deceptively quiet and small.

On auscultation, there is often a presystolic sound, due to right atrial hypertension, best heard over the right ventricle and atrium. The first sound is followed by an early systolic click and short ejection murmur due to blood entering the dilated pulmonary artery under high pressure. The second heart sound is very narrowly split, and may appear single, but the pulmonary component can usually be separated from the aortic by deep inspiration, and is strikingly increased in intensity. A faint high-pitched short early diastolic murmur may be heard in the second and third left intercostal spaces if pulmonary valve incompetence is present.



[illegible] ponent increased (A = aortic valve closure, P = pulmonary valve closure)

A pansystolic murmur, increasing on inspiration, at the tricuspid area is present if tricuspid incompetence has occurred. Fig. 18b shows the phonocardiogram in severe pulmonary hypertension Signs of underlying heart disease, such as mitral stenosis, should be looked for, although if the pulmonary resistance is really high, the left atrial flow may be so restricted as to fail to produce the characteristic obstructive mitral murmurs and sounds. This "silent" type of mitral stenosis will be discussed further in Chapter 8.

It will be realized that the foregoing description applies to extreme arterial hypertension and that lesser degrees will show fewer signs. The atrial sound may be absent, the right ventricle only slightly enlarged, and the pulmonary closure sound moderately increased. Only in severe cases are the signs of a low cardiac output clinically striking.

The cardiogram shows varying degrees of right ventricular, and often of right atrial hypertrophy, with sometimes a prolonged PR interval. The cardiographic signs will be fully discussed in Chapter 7.

The radiological signs of pulmonary hypertension vary considerably according to the cause and will be fully described in Chapter 5.

stenosis the face is often moon shaped, while in severe pulmonary hypertension it is gaunt and with high colour in the cheek bones. The radiological appearances are discussed in Chapter 5.

Diagnosis of severe pulmonary hypertension from the Tetralogy of Fallot may be difficult when cyanosis is slight, for in the Tetralogy, the aortic valve sound is well heard, and the pulmonary frequently inaudible, while the systolic ejection murmur may be quite soft, and end before the aortic sound, as a result of the overriding aorta and ventricular septal defect. However, the "a" wave of the venous pulse is small, and the cardiogram sometimes shows less florid right ventricular hypertrophy.

The signs of right atrial hypertrophy and hypertension, augmented jugular venous "a" wave, atrial sound and large right atrium can result also from obstruction to right ventricular inflow, best exemplified by tricuspid valve stenosis. The cardinal clinical differences lie in the right ventricular impulse and last portion of the jugular venous pulse. In tricuspid stenosis the right ventricle is quiet and the left ventricle can easily be felt, while the "y" descent of the jugular venous pulse is slow, indicating delayed right ventricular filling. A tricuspid mid-diastolic murmur, which increases in inspiration, is usually heard at the tricuspid area. The second heart sound is normal unless pulmonary hypertension co-exists, in which case the right ventricle will be enlarged and the clinical diagnosis may have to rest upon the character of the jugular venous pulse and the tricuspid murmur A systolic murmur is often heard in tricuspid stenosis, especially when atrial fibrillation is present, due to associated tricuspid incompetence. This murmur is maximal at the tricuspid area and conducted up the sternum and towards the cardiac apex, and is full length, rather than ejection, in type. Atrial fibrillation is probably more common in tricuspid stenosis than in severe pulmonary hypertension, whatever the cause The cardiogram in dominant tricuspid stenosis shows right atrial without right ventricular hypertrophy. Radiologically, the only abnormality may be the large right atrium

Constrictive pericarditis may cause difficulty in clinical differentiation, for the venous pressure is raised and the "a" wave prominent but not significantly overreaching the "v". The "x" and "y" descents are sharp. The venous pressure rises on inspiration. The right ventricle is normal, the heart small and quiet, the second heart sound soft. The ejection click is absent, and there is a well-marked third heart sound Pulsus paradoxus, calcification of the pericardium, and a cardiogram showing generalized low voltage and T wave inversion make the distinction easier Fig 20 shows diagrammatically the differential diagnosis based on auscultation and the jugular venous pulse.

2. Cardiac catheterization. Frequently, however, cardiac catheterization with measurement of pulmonary vascular pressures and flows is necessary to confirm the diagnosis [illegible]

between right ventricle and right atrium as would occur with tricuspid stenosis.

For the correct interpretation of pulmonary hypertension, it is essential to relate pulmonary pressure to flow It is necessary to calculate pulmonary vascular resistance, and this may crudely be done by applying the formula: $\frac{P}{F}=R$, where P=Mean arterial pressure, F= Pulmonary flow in litres/min and R=Resistance. This gives an approximation of the

as thyrotoxicosis, has already been quoted. Reduction of left atrial hypertension by successful mitral valvotomy is followed by a further reduction in pulmonary vascular resistance and arterial pressure (Chapter 8). It may therefore be said that when pulmonary vasoconstriction or excessive flow can be relieved (usually by surgical means), then the prognosis is good. When, however, the pulmonary vascular bed is obliterated, or the lung parenchyma severely damaged, the prognosis is grave. Thus, for example, when the arteriolar bed is filled with minute emboli, relentless pulmonary hypertension develops, and is followed by progressive right ventricular failure and death in a few months, or at the most, years. The same sinister course occurs in cases of idiopathic pulmonary hypertension in which extensive obliteration, rather than constriction, of the pulmonary arteriolar bed has occurred (Chapter 12).

The prognosis in patients with the Eisenmenger Reaction (congenital pulmonary hypertension and right-to-left shunt) is better, and patients with ventricular septal defect or patent ductus with right-to-left shunt may live until middle age This is probably because the defect acts as a "safety valve" and prevents the pulmonary artery pressure from exceeding the systemic, thus protecting the right ventricle somewhat. When the ventricular septum and ductus are closed, the right ventricle is forced to work against an intolerable resistance, so that the pressure rises to well above systemic levels, with resultant right ventricular failure. In patients with atrial septal defect, the Eisenmenger reaction occurs late, and the prognosis is then usually poor (Chapter 9).

Whatever the cause, the gravity of the prognosis is directly related to the severity of the hypertension, but it is wise to regard appreciable pulmonary hypertension as a potentially serious disease which should not be allowed to go untreated. There is no pulmonary counterpart of benign systemic hypertension Furthermore, irreversible changes in the pulmonary vessels may occur as a result of prolonged hyperdynamic and vasoconstrictive hypertension, and the severe hypertension may be aggravated by secondary pulmonary vascular obstruction.

The Diagnosis of Pulmonary Hypertension

1. Clinical. The diagnosis can be made at the bedside in many cases, especially the more severe ones, and the clinical picture is an easy one to recognize. It must be stressed, however, that most of the signs of pulmonary hypertension are in fact produced by right ventricular and right atrial hypertension. Thus the enlarged right ventricle, right atrial sound, augmented "a" wave in the jugular venous pulse, small arterial pulse, and electrocardiogram may be identical both in severe pulmonary stenosis with normal aortic root and closed ventricular septum and in idiopathic pulmonary hypertension. In either case the presence of digital clubbing and central cyanosis may be the result of a right-to-left shunt through a patent foramen orale.

The differential diagnosis can be made on the other auscultatory findings In pulmonary stenosis the short soft ejection murmur of pulmonary hypertension is replaced by a loud long ejection murmur and thrill, and the second heart sound is widely split, with a very soft, sometimes inaudible, pulmonary valve component. The systolic murmur frequently passes through the aortic valve component and runs up to the pulmonary, giving the impression of a diastolic murmur. The patients' faces may give a clue, for in pulmonary

$$\text{Total pulmonary Vascular resistance} = \frac{\text{Mean pulmonary artery pressure mm./Hg}}{\text{Pulmonary blood flow in litres/min.}} = \text{units}$$

$$\text{Pulmonary arteriolar resistance} = \frac{\text{Mean pulmonary artery pressure } \textit{minus} \text{ mean left pulmonary capillary ``wedge'' pressure}}{\text{Pulmonary blood flow in litres/min.}} = \text{units}$$

These calculations of resistance are of course gross oversimplifications of a very complicated situation (Chapter 2) The equation, while valid for a system of tubes of fixed calibre, takes no account of variable flow in a highly complex vascular bed capable of adapting itself rapidly to changes of flow and pressure over a wide range or of the influence of pulmonary blood volume. However, this measurement will continue to be used until

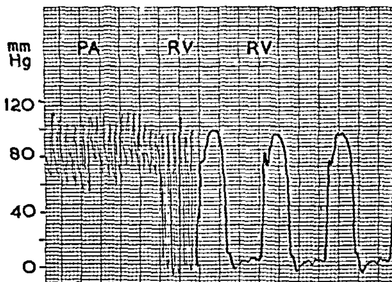


Fig. 21 Continuous pressure pulses from pulmonary artery (PA) and right ventricle (RV) in severe pulmonary arterial hypertension There is no appreciable pressure gradient across the right ventricular outflow tract

better ones become available It should not be credited with a degree of accuracy which it does not possess.

Calculated in this way, the normal pulmonary vascular resistance is around zero, the maximum normal being 2 5 units. Five units constitutes moderate and over ten units extreme, obstructive hypertension It is implicit from the measurement that the higher the resistance, the higher the pressure and the lower the flow. When hypertension is solely hyperdynamic, the resistance is normal because both flow and pressure are high. Calculation of pulmonary and systemic flows in patients with intracardiac shunts will be discussed in Chapter 9

3. Differential diagnosis. Having made a diagnosis of pulmonary hypertension at the bedside by clinical examination aided by radiology and cardiography, it is necessary to determine the cause. Hyperdynamic hypertension can usually be detected without difficulty, especially if the combination of large arterial pulse and warm extremities with

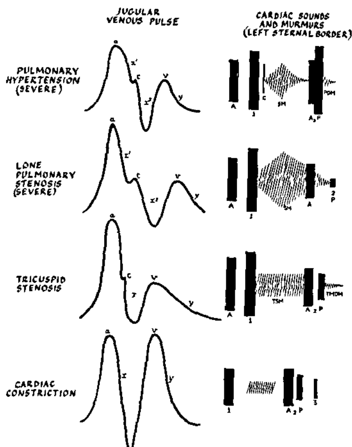


FIG 20 Diagram of jugular venous pulse and heart sounds and murmurs in pure pulmonary stenosis, severe pulmonary arterial hypertension, tricuspid stenosis and cardiac constriction, all in sinus rhythm (Not to scale)

a = atrial contraction
c = c wave
x^1, x^2 = x descents
v = atrial filling wave
y = y descent (see text)
A = atrial sound
c = click
SM = ejection systolic murmur
1 = 1st heart sound
2 = 2nd heart sound
A = (aortic valve closure)
P = (pulmonary valve closure)
3 = 3rd heart sound
TMDM = tricuspid mid-diastolic murmur
TSM = tricuspid pansystolic murmur

total pulmonary vascular resistance. Pulmonary arteriolar resistance may be calculated if the pulmonary venous pressure is obtained indirectly by wedging the catheter in a small branch of the pulmonary artery, and subtracted from the mean arterial pressure (Chapter 8).

It is thus apparent that the principal treatment of pulmonary hypertension is surgical and that the best results are to be expected in patients with vasoconstrictive and hyperdynamic hypertension. Surgery has little part to play in the relief of obliterative hypertension, as might be expected In the Eisenmenger syndrome (Chapter 9), closure of the septal defect or ductus is rarely beneficial, and may be fatal, for the safety valve has been removed

When vasoconstrictive hypertension is due to chronic hypoxia resulting from lung disease, the pressure can be reduced if the arterial saturation can be increased (Mounsey *et al*, 1952) Oxygen therapy, judiciously applied (Chapters 10 and 11) may lower the pressure, and antibiotics and bronchodilators are also of great importance. In chronic hypoxic cor pulmonale, depression of thyroid function is said to produce some improvement by reducing tissue oxygen consumption and thus increasing the oxygen content of mixed venous blood (Daley, 1957). Personal experience, however, has been disappointing.

When obliteration of the pulmonary vascular bed has resulted from thrombo-embolism, then long-term or permanent anticoagulant therapy is rational treatment, and offers the only prospect of improvement, or at least of preventing further thrombosis If the disease can be diagnosed early, prolonged anticoagulant treatment may be followed by resolution of the pulmonary hypertension and is therefore of the first importance In patients with obliteration or obstruction from other causes, anticoagulants have been given to prevent the onset of thrombosis which could be precipitated by sluggish blood flow through diseased pulmonary vessels

Attempts to produce pulmonary vasodilatation by means of drugs have been disappointing. Ganglion blocking agents and adrenergic blocking agents have been used with little success. Although tolazoline often reduced the pulmonary arteriolar resistance in acute observations, little evidence is available to indicate that it is of value as long-term therapy. The same is true of hexamethonium Dibenylene injected into the pulmonary artery of dogs abolishes the pressor effect of nor-adrenaline (Daley, 1957), but there is no proof of its efficacy as a therapeutic agent It should in any case be avoided in subjects with tendency to wheeze, since its adrenergic blocking properties may induce bronchospasm. Aminophyllin may be of some slight value, and has been shown to lower pulmonary arteriolar resistance at cardiac catheterization It has the advantage of additional cardiotonic and bronchodilator effects

Cortisone may be tried in patients with evidence of pulmonary arteritis, but its effect is unpredictable

Sympathectomy or ganglionectomy has been attempted but without notable success, and in one case of idiopathic pulmonary hypertension was strikingly ineffective (Gorlin *et al*, 1958)

There is thus little effective therapy for obliterative hypertension, and the clinician often remains impotent as the remorseless progress of the disease produces increasing right ventricular failure Then digitalis, and low salt diet, and diuretics are of value. It should be clearly understood that such treatment is merely closing the stable door after the horse has bolted and only aims at ameliorating the complications of the disease, leaving the disease itself unchanged.

At the present time, therefore, hyperdynamic and vasoconstrictive hypertension have a good prospect of relief by surgical means which remove the precipitating cause, if not

a raised venous pressure is kept in mind as indicating a hyperdynamic circulatory state. In many cases of severe obstructive hypertension, however, the cause may not readily be apparent. It is vital therefore to decide whether the arterial hypertension is primary or secondary to venous hypertension. Severe dyspnoea, especially paroxysmal, always suggests venous hypertension, whereas tiredness, fainting and anginal pain suggest a high arteriolar resistance. Signs of mitral valve obstruction, which may have to be diligently sought, may answer this question, but the most helpful clinical indication of the presence of venous hypertension is careful examination of a good postero-anterior radiograph of the chest (Chapter 5). It should be remembered that although mitral valve disease is the commonest cause of a mitral obstructive murmur enlargement of the left atrium and pulmonary venous hypertension, other conditions such as left atrial tumour can produce the same picture (Chapter 8). Left ventricular failure due to systemic hypertension, coronary artery disease, or aortic valve disease may also produce radiological signs of pulmonary venous hypertension (Chapter 5) However, these last conditions seldom present a clinical picture which is dominated by the signs of pulmonary arterial hypertension

Final proof of pulmonary venous hypertension is obtained by finding an elevated pulmonary capillary venous pressure, and this should always be sought, although often hard to obtain when the small pulmonary arteries are markedly narrowed.

If evidence of pulmonary venous hypertension is lacking then the obstruction lies primarily in the arteriolar bed, and the cause may be congenital heart disease (Eisenmenger reaction), chronic lung disease, thrombo-embolism, pulmonary arteritis, or idiopathic pulmonary hypertension. The diagnosis of the Eisenmenger reaction will be considered in Chapter 9. Thrombo-embolic hypertension is suggested by a history of calf vein thrombosis, or pulmonary infarction and pleural pain, but may be completely silent Tests for auto-immunization and Collagen diseases may reveal evidence of a specific pulmonary arteritis The diagnosis of chronic lung disease and cor pulmonale will be considered in Chapters 10 and 12, and of idiopathic pulmonary hypertension in Chapter 12

The cardiogram is not usually of value in distinguishing between different types of precapillary pulmonary hypertension, but the presence of left atrial P waves is a valuable guide to the presence of left atrial hypertension. Some form of right bundle branch block may suggest an atrial septal defect, while in thrombo-embolic hypertension, T wave inversion in right praecordial leads may be striking (Chapter 7).

Radiologically, signs of bronchiectasis or pulmonary fibrosis may help to establish the presence of underlying lung disease as the cause, or there may be evidence of a left-to-right shunt indicating congenital heart disease (Chapter 5)

The Management of Pulmonary Hypertension

The essential basis of treatment of pulmonary hypertension is removal of the cause. [illegible] which [illegible] rten-sion when a septal defect is closed surgically (Fig. 19)

Relief of pulmonary venous hypertension by mitral valvotomy frequently leads to a fall in arterial pressure and resistance and provides another striking example.

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delayed until irreversible changes have occurred. Obliterative hypertension is virtually untreatable, except by anticoagulants, which may be combined with one or more vasodilators in the hope that the progress of the disease may be halted.

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significant alteration in the nomenclature or interpretation have been suggested and no further important papers have appeared except for one by Herrnheiser (1951). This author confirmed Lodge's observations and in some detail describes many normal variations of the segmental anatomy of the pulmonary arteries and veins in their arrangement of supplying the various bronchopulmonary areas of the lung.

The study of post-mortem corrosion specimens has led Lodge and most other workers to the conclusion that the radiological anatomy of the pulmonary arteries follows very closely the anatomy of the bronchial tree. The only important variations are found in the upper lobes where arterial branches may arise separately from the main upper lobe artery—the so-called "tree-type" of Herrnheiser, or where they arise from a common origin, the "bush-type" (Fig. 22). Lodge added a third variety, a mixture of the tree and bush. The

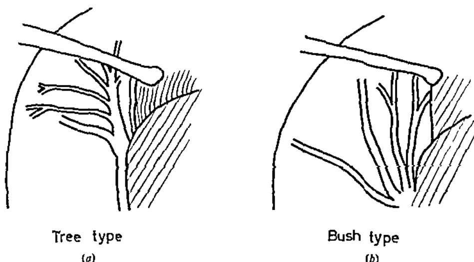


FIG 22. Diagrammatic representation of the upper lobe arterial patterns: (a) "Tree-type", (b) "Bush-type". (After Lodge.)

pulmonary veins do not bear a close relationship to the bronchi, they tend to cross the bronchi and pulmonary arteries at varying angles, and never run parallel to them.

A very detailed purely anatomical description of the vascular anatomy of the lung can be found in Miller's monograph, "The Lung" (1947), and in Boyden's book, *Segmental Anatomy of the Lung* (1955).

Based on Lodge's description of the pulmonary vessels the following pattern with a somewhat modified terminology is suggested which is in conformity with the bronchial terminology.

The Main Pulmonary Arteries

Normally the greater part of the middle segment of the left mediastinal border is formed by the main pulmonary artery. The right main pulmonary artery is longer than the left and passes behind the superior vena cava It enters the lung anterior to the right main bronchus and then immediately divides into the right upper lobe artery and the intermediate artery which in turn gives off the branches for the middle and lower lobes.

CHAPTER 5

THE RADIOLOGY OF THE PULMONARY CIRCULATION

BY R. E STEINER

IN this chapter the radiological appearances of the heart and lungs, in so far as they are connected with the pulmonary circulation, will be described and correlated with clinical, physiological and pathological data recorded in the other sections of the book.

Since the radiological interpretation of the pulmonary vessels largely depends on an understanding of the normal and pathological radiological anatomy, it is intended in the opening remarks to describe the radiological anatomy of the pulmonary arteries and pulmonary veins

THE RADIOLOGICAL ANATOMY OF THE PULMONARY ARTERIES AND VEINS

The advent of radiology at the turn of the century made a new method available for the study of lung anatomy. For the first time it was possible to see the lung vessels topographically before dissection and to establish their relationship to the bronchi and the various lung segments and sub-segments Numerous papers have been written both by anatomists and radiologists in the past sixty years, referring to the radiological anatomy of the pulmonary vessels and the bronchial tree. The first accurate and complete anatomical description of the bronchi, pulmonary arteries and veins in English dates back to Ewart's monograph in 1889 In 1922 the French radiologist Garcin was able to show that the branching linear shadows seen on radiographs were in fact vascular and not due to bronchial shadows.

The first radiological studies of the pulmonary vessels in the living were not made until 1931 when Moniz *et al* injected a highly concentrated solution of sodium iodide into the right atrium and were able to take films of the lungs as the contrast material outlined the pulmonary vessels Independently Forssman (1931) reported a very similar technique of examination. Tomography, another method for the radiological study of lung structures and particularly of pulmonary vessels, was described by Twining (1931). It was only in 1936 that Herrnheiser referred for the first time to the homology of the vascular supply of the right and left lungs and adopted a similar nomenclature for the vessels on both sides. Herrnheiser's fundamental work at that time laid the cornerstone of the study of the radiological anatomy of the pulmonary vessels; the same author in the following years added many papers to the literature, enhancing our knowledge of the pulmonary circulation. The first paper correlating the radiological anatomy of the pulmonary vessels in post-mortem injection studies with their appearance on plain radiographs of the chest in the normal and abnormal was presented by Lodge (1948). Since its publication no

Right Upper Lobe Veins

(1) Apical.
(2) Anterior.
(3) Posterior.
(4) Medial.

The veins descend medially towards the mediastinum crossing the segmental upper lobe arteries and the intermediate artery until they unite into one trunk which enters the left atrium at the ostium of the superior pulmonary vein (Fig. 23).

Right Middle Lobe Artery

(1) Medial.
(2) Lateral.

Right Middle Lobe Veins

(1) Medial.
(2) Lateral.

Right Lower Lobe Arteries

(1) Apical.
(2) Retro-cardiac.
(3) Anterior basal.
(4) Lateral basal.
(5) Posterior basal.

Right Lower Lobe Veins

(1) Apical.
(2) Anterior basal
(3) Anterior axillo-basal.
(4) Posterior basal.
(5) Posterior-axillo-basal.

These five veins extend cranially and medially to unite with the middle lobe veins crossing the segmental arteries on their course and finally enter as a single vein the left atrium at the ostium of the inferior pulmonary vein (Fig. 23).

Arteries and Veins of the Left Lung

With few exceptions the anatomy of the pulmonary arteries and veins on the left and right side is identical.

(1) Right upper lobe is similar to the left upper lobe, excluding the lingula.
(2) Right middle lobe is similar to the lingula of the left upper lobe.
(3) Right lower lobe is similar to the left lower lobe.

Variations may, however, occur in the apical segment supplied by the posterior apical artery (Fig. 23).

The left main pulmonary artery is very short and arches to the left towards the hilum of the lung where it branches into the upper and lower lobe arteries.

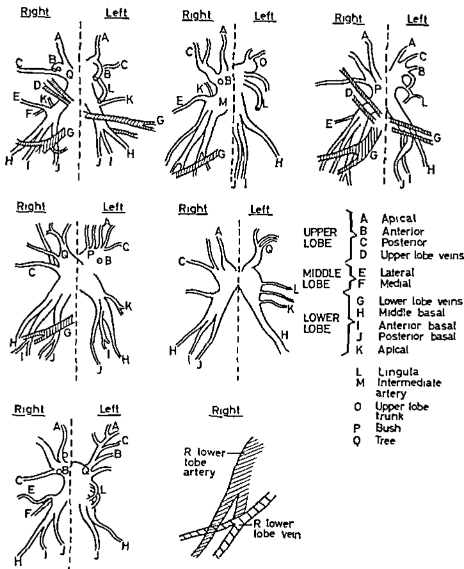


FIG 23 Diagrammatic representation of the radiological patterns of the larger pulmonary arteries and veins. (Modified after Lodge.)

Right Upper Lobe Arteries

(1) Apical.
(2) Anterior.
(3) Posterior.

Variations in size and origin of the three vessels are common and so are their number. There may be more than the three basic vessels or less (Fig. 23).

The Bronchial Arteries

The bronchial arteries are of such a small calibre that they are invisible on a straight radiograph of the chest of normal subjects. Even by employing such methods as tomography or angiography it is not possible to demonstrate these vessels. A comprehensive description of the bronchial artery anatomy can be found in Miller's monograph "The Lung". The normal radiographic anatomy on post-mortem injected lungs has been studied by Cudkowicz and Armstrong (1951) The radiological appearances of the bronchial arteries in pathological states will be discussed later.

The Pulmonary Lymphatics

The pulmonary lymphatics, like the bronchial arteries, are too small to be visible radiographically in normal chest radiographs. For a comprehensive anatomical description of the pulmonary lymphatic system the reader is referred to Miller's monograph "The Lung". The appearances of the pulmonary lymphatics in pathological conditions will be discussed later.

RADIOLOGICAL TECHNIQUES FOR INVESTIGATION OF THE PULMONARY CIRCULATION

The Plain Films of the Chest

Good radiography of the chest is essential for the study of the pulmonary vascular pattern. A contrasty film is preferable to a soft radiograph The film must be just sufficiently penetrated to outline the vascular markings behind the heart. Slight obliquity or unequal compression of the soft parts against the cassette may obscure the hilar shadows or produce haziness, thus diminishing contrast and blurring the finer lung vascular detail Postero-anterior radiographs must be taken at six feet distance to avoid magnification and radiographic factors should be so chosen as to give a short exposure time to diminish blurring due to the patient's movement or cardiac pulsation. The following factors are considered satisfactory. 10–12 mAS at 65–75 kV. for a P.A. chest film, or alternatively a high kV. technique working at 120–130 kV. and 1–2 mAS.

The standard postero-anterior film is most useful for comparison of the vascular pattern on the right and left side of the chest, for the assessment of the main pulmonary artery and its main branches and for the study of hilar shadows and the smaller peripheral pulmonary vascular branches.

The technical considerations discussed above apply also to the oblique and lateral radiographs. These views are most useful for the demonstration of the main pulmonary artery and its main right and left branches as well as the hilar shadows. In these projections the main pulmonary artery is seen to arise from the right ventricle anteriorly, curves upwards and backwards and divides into the right and left main branches at the same level as the bronchial bifurcation. The left main pulmonary artery can be seen to divide further into its main branches, whereas the right main pulmonary artery on the lateral radiograph appears as an oval shadow just below the bifurcation of the bronchi and anterior to the right main bronchus.

Lodge has shown in studies of the plain chest radiograph that a large number of pulmonary vessels can be accurately identified according to their various anatomical patterns. Arteries are much more easily seen than the veins, except for the lower lobes where the veins are as readily seen. Pulmonary veins usually present a less dense and clear-cut shadow, and as a rule, they appear to be thicker than the corresponding arteries.

Vascular shadows diminish gradually in calibre in proportion to their distance from the hilum. The tributary vessels are always of smaller calibre than the primary vessel.



FIG 24 (a and b). (a) Angiographic demonstration of the normal pulmonary arteries (venous angiocardiogram) (b) Angiographic demonstration of the normal pulmonary veins (venous angiocardiogram)

Shadows caused by blood vessels are either straight or gently curved but in normal patients never tortuous. They cast a moderately dense shadow with well-defined edges. When seen end-on they appear either circular or elliptical and are often closely related to the adjacent bronchus. This description of the normal vascular anatomy on plain radiographs of the chest is very similar to that seen on tomographic studies, and is even more striking, on pulmonary angiograms (Figs. 24a and 24b). When the pulmonary vessels are filled with contrast material they are outlined very sharply and distinctly.

By whichever radiographic procedure the lung vessels are studied, the limitations of the methods make it impossible to analyse the small peripheral branches at the extreme edge of the lung. It is only possible to assess satisfactorily the main arteries and veins and their major branches to a level of about the fourth and fifth divisions.

Pulmonary Angiography

The pulmonary vessels can be demonstrated radiologically by contrast studies and this can be achieved in two ways:

(1) Venous angiocardiography.
(2) Selective pulmonary arteriography.

The first method is the one more frequently used, and the one originally described by Moniz *et al.* (1931). This method was further developed by Robb and Steinberg (1938); Chavez *et al.* (1947); Goodwin *et al.* (1952)

In 1949 Jónsson *et al.* described a new technique of selective angiocardiography in which contrast material was injected through a cardiac catheter into the right atrium, into the out-flow tract of the right ventricle, or into the main pulmonary artery. Their object in injecting the contrast material into the pulmonary artery was not so much an attempt to outline the pulmonary vessels, but rather to obtain better concentration of contrast material on the left side of the heart for the study of the left atrium, ventricle and aorta. Once this new method had been established it was not long before the procedure was used primarily for the study of the pulmonary vasculature. (Bolt *et al.* 1951). In the following years the use of selective pulmonary arteriography was further extended and has now become the method of choice for the radiological study of the pulmonary arteries and veins, Steiner and Goodwin (1954); Doyle *et al.* (1957); Bolt *et al.* (1957); Arvidsson and Odman (1957)

The technique of venous angiocardiography, when contrast material is injected through a cannula into the antecubital vein or through a polythene catheter into the iliac or subclavian vein, or more proximally into the superior inferior vena cava, is used to study the pulmonary vasculature only if the selective method is impracticable. In very small children, where selective catheterization may be too difficult, or in adults where pulmonary artery catheterization has failed the original method of venous angiocardiography may have to be resorted to and the injection made into the cava or right atrium. This method may also be of some use in the investigation of anomalous pulmonary venous drainage and this will be discussed later. The radiological details of venous angiocardiography will be briefly described.

Venous Angiocardiography

By this technique contrast material is injected as rapidly as possible either through a Robb-Steinberg cannula into the antecubital vein, or alternatively through a polythene catheter into a brachial vein or superior vena cava, or through the inguinal vein into the inferior vena cava The amount of contrast material injected is not more than 1·5 ml. per kg. of body weight in children and 1–1·2 ml. per kg. of body weight in adults. It is essential that the contrast material is injected as rapidly as possible; for this purpose a mechanical injection device should be used such as a Gidlund pump (1956) or Pattinson Somerville pump (1958). With these devices it is possible to inject 20–30 ml contrast material per sec. Since the procedure is aimed at demonstration of the pulmonary vessels the patient is examined in the antero-posterior position. The X-ray films must be of a size large enough to cover both lung fields completely, *i e.* 15 in. × 12 in. or 14 in. × 14 in., and an adequate number of films must be exposed at the appropriate time to cover the

Fluoroscopy

In the study of the pulmonary vasculature fluoroscopy of the chest serves two main purposes.

(1) To assess the main pulmonary artery size in the oblique and lateral projections and also to ascertain the optimum position of the patient for the taking of the oblique radiographs. A barium swallow is helpful since the right main pulmonary artery lies close up against the right main bronchus and the bronchus in turn lies in close proximity to the oesophagus. The barium-filled oesophagus will thus be impressed anteriorly and just below the aortic arch by the right main bronchus and pulmonary artery. The degree of this impression varies with the size of the right main pulmonary artery.

(2) To assess pulmonary artery pulsation. This is best done by keeping the radiographic beam to a very small size and coning down to an aperture of approximately 1–2 cm^2, centering on one of the main pulmonary artery branches at the right hilum and observing the vessel carefully. Intrinsic pulsation will be easily recognized if the vessel exhibits density variations coincident with every heart beat and at the same time appears to expand and contract. This can equally well be seen on a longitudinal section of the artery or on end-on vessels. As will be discussed later, intrinsic pulsation should also be looked for in the peripheral lung fields at the level of second- and third-order pulmonary artery branches.

SPECIAL METHODS OF INVESTIGATION

Tomography

This can be done in the antero-posterior, lateral and oblique positions. This method is of great value in demonstrating major pulmonary arteries at any selected level within the lung, in any given plane, and is a particularly valuable method for the study of the hilar structures. Michelson and Salik (1959).

Since a large number of tomographic sections are required to demonstrate the major pulmonary vessels at various levels within the lung, and since a relatively large area of the chest will be exposed to radiation, the use of a multi-section tomographic device is advisable. The multi-section technique causes considerably less radiation to the patient than single film tomography without undue loss of quality to the individual films.

In the antero-posterior projection the tomographic sections should be so arranged that the middle cut lies at hilar level and the remaining films should cut at 1 cm. intervals through the mediastinum and lungs above and below the hilum. When the multi-section technique is used up to seven films can be exposed at once and a slab of tissue 7 cm. in thickness can be thus analysed. The following radiographic factors are suggested for the antero-posterior technique: 70 mAS., 85–87 kV. The technique adopted for the lateral and oblique projections is very similar to that in the antero-posterior projection, except that two-thirds of the film should be cut through the lung above the hilar level and only one-third of the films through the hilum and mediastinum, below the hilar level. For the oblique and lateral projections the following radiographic factors are suggested: 70 mAS., 98–100 kV.

Positioning of the catheter must be controlled under careful fluoroscopy. The examination can be done under general anaesthesia, or heavy sedation; the latter is perfectly adequate since the newer contrast materials are well tolerated by the patient

Since cardiac catheterization is usually carried out with the patient's arm only slightly abducted and since the injection of contrast material is usually done with the arm in marked abduction it is essential to check the catheter position finally with the arm abducted, and should an end-hole catheter be used adequate allowances must be made for the possible whip-back during injection. For instance, if the main pulmonary artery is to be injected the catheter tip should lie halfway across the right main pulmonary artery; it would then probably recoil into the main pulmonary artery during injection.

Contrast Material

One of the most suitable contrast materials at present is 85 per cent Hypaque (3.5-di-(acetylamino-)-2.4·6-triiodbenzoate) or any equivalent substance. The quantity to be injected depends entirely on the patient's weight and on the injection site. If the injection is made into the main pulmonary artery 0·75 ml. per kg of body weight are used. If the injection is made into the right or left pulmonary arteries 0 5 ml. per kg of body weight are adequate. For segmental injections the quantity must be further reduced to about 0 25 ml. per kg of body weight; or if the catheter is in the wedged position, 3–4 ml. of 85 per cent Hypaque are perfectly satisfactory. As in venous angiocardiography, rapid injection is very important with the exception of the catheter in the wedged position The contrast materials are of rather high viscosity and since a high speed of injection is essential, preliminary preheating of contrast material before the injection is most important. This will diminish viscosity and improve flow.

Radiographic Procedure

This is the same as for venous angiocardiography except for the following points:

(1) Exposure of films must be started just before the injection commences
(2) The area to be radiographed should be limited to the tributary field of the pulmonary artery injected, *i e.* only the right lung will need to be X-rayed if the injection is made into the right main artery.
(3) Oblique projection may be at times of great value and more useful than routine A.P. views, particularly when small segmental arteries are injected, and also for the left lower lobe, to separate it from the heart shadow

THE RADIOLOGICAL APPEARANCES OF THE PULMONARY ARTERIES AND VEINS IN PATHOLOGICAL CONDITIONS

A careful study of the radiological appearances of the lungs can frequently present information of the greatest value in the diagnosis and prognosis of disordered lung function be it due to heart or pulmonary disease. It is possible to correlate the radiological appearances seen on chest radiographs, and more convincingly on angiographic studies, with the haemodynamic findings, the clinical picture of the patient, and also with

pulmonary circulation and to outline the pulmonary arteries and veins. Although manually operated cassette changers are adequate to produce the required number of films and to cover the circulation, mechanical film changers such as the Schönander or Elema units are far superior. With these devices films can be exposed at a rate of up to 6–12 per sec. The exposure rate of four to six films per second for six to eight seconds is adequate for practical purposes. Basic radiographic factors adults 120 kV., 8–10 mA ; children 120 kV., 2–4 mA

If the injection is made into a peripheral vein exposure of films should not be started until the end of the injection If, however, the injection is made into the inferior vena cava or superior vena cava the exposure should be started at the beginning of the injection. If this scheme is followed the right cardiac chambers, the pulmonary vessels and also the left atrium and ventricle will be outlined Usually the examination need be done in only one plane In exceptional circumstances, however, lateral and oblique projections may be required, in which case a bi-plane serial unit is of great help The indications for a bi-plane examination will be referred to later in the text.

Selective Angiocardiography

By this method contrast material is injected into the pulmonary artery through a cardiac catheter. When selective pulmonary arteriography is to follow immediately after cardiac catheterization, it is preferable to use a cardiac catheter with side-holes rather than the standard Cournand catheter with a single end-hole. The Lehman catheter, or its modification with a blocked end-hole is most suitable for this procedure. The use of the side-hole catheter prevents whip-back during injection. Thus injection of contrast material at the wrong site is avoided and also damage to the endocardium of the heart or intima of the pulmonary artery by the jet of contrast. The catheter can be placed either in the main pulmonary artery just above the pulmonary valves, or into the right or left main pulmonary artery. The largest bore catheter, such as a No. 8 or No. 9 Lehman catheter, should be used to make fast injection possible.

If contrast material is injected into the main pulmonary artery the vasculature of both lungs can be studied, alternatively, if the injection is made into the right or left main pulmonary artery only one lung can be examined. The catheter can also be advanced further out into a main peripheral segmental branch of the pulmonary artery, thus obtaining a segmental opacification of the pulmonary vessels either of the whole lobe or lobar-sub-segment. Injection of contrast material with the catheter in the wedge position in a small peripheral artery should not be done under pressure since this may give rise to complications such as pulmonary oedema or infarction, Bolt *et al.* (1957) and Loomis-Bell *et al.* (1959). These authors have shown, however, that with careful slow manual injection peripheral segmental arteriography with the catheter in the wedge position can be done quite safely. Nevertheless, it is wise to proceed with caution, particularly in patients with pulmonary hypertension and pulmonary stenosis (McAffee, 1955). One case of pulmonary oedema due to selective pulmonary angiography was reported by Besterman *et al* (1956) in a patient with pulmonary hypertension, probably of the idiopathic variety. These authors attributed to oedema to a sensitivity reaction to the drug; intravenous infusion of hydrocortisone produced a rapid recovery in this patient.

EXTREME HIGH OUTPUT STATES

The radiological appearances of the lungs and in particular of the pulmonary vessels are often quite normal in this group. Occasionally there may be evidence of some dilatation of the main pulmonary artery and its main branches producing some fullness of the hilar shadows. Rarely is there any significant hyperaemia in the peripheral lung field. On fluoroscopy vigorous pulsation of the heart and only slight intrinsic hilar pulsation of the main pulmonary arteries indicating a greatly increased blood flow and slightly elevated pulmonary artery pressure can be noted.

There may be slight cardiac enlargement involving particularly the right ventricle and this can fluctuate with variations in the patient's conditions—for example, improvement in the patient's anaemia may cause a dilated heart to diminish in size and pulsation of the pulmonary vessels to become less vigorous.

TORRENTIAL PULMONARY BLOOD FLOW DUE TO LEFT TO RIGHT SHUNT WITHOUT INCREASED PULMONARY VASCULAR RESISTANCE

When pulmonary blood flow exceeds about three times the normal, *i.e.* 20–30 litres/min, a rise in the pulmonary artery pressure often follows (see Chapters 4 and 9) and a number of radiological features which are common to all conditions listed in this group,

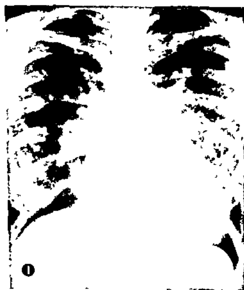


FIG 25a. [illegible] P.A. chest film of [illegible]



FIG. 25b. Same patient as Fig 25a After operation closure of the atrial septal defect Diminution in size of the main pulmonary artery and its main branches The smaller peripheral arteries are of normal size; no longer evidence of pulmonary hyperaemia.

pathological studies. Since the pulmonary circulation is so closely related to hea lung function it is important from a radiological point of view not only to stu pulmonary appearances, but also the heart itself and to look upon both structure single functioning unit. In the following discussion of the various disorders affecti pulmonary circulation, main emphasis will be placed on the radiological appearan the lungs and at the same time the heart will also be considered, but in less detail.

PULMONARY HYPERTENSION

On consideration of the classification of pulmonary hypertension discussed in Cha it will be seen that on radiological grounds a very similar classification can be acc One can thus recognize the pulmonary vascular pattern associated with:

(A) Pulmonary Arterial Hypertension

This can be further divided into.

(i) Hyperdynamic pulmonary hypertension due to increased pulmonary blood
(ii) Obstructive pulmonary hypertension due to increased pulmonary resistanc decreased pulmonary blood flow.

(B) Pulmonary Venous Hypertension

This is often complicated by an increased pulmonary vascular resistance giving r a secondary pulmonary arterial hypertension (see Chapter 4).

RADIOLOGICAL APPEARANCES OF PULMONARY ARTERIAL HYPERTENSION DUE TO INCREASED BLOOD FLOW

The Causes of Increased Blood Flow

(1) *Extreme high output states.*

(*a*) Anaemia.
(*b*) Pulmonary heart failure.
(*c*) Thyrotoxicosis.
(*d*) Arteriovenous fistula.
(*e*) Paget's disease.
(*f*) Liver failure.

(2) *Left to right intracardiac or aortic pulmonary shunt causing torrential pulmo blood flow.*

(*a*) Patent ductus arteriosus
(*b*) Aortic pulmonary septal defect.
(*c*) Atrial septal defect.
(*d*) Ventricular septal defect.

in the heart and lungs seen on the chest radiographs of patients in this group are summarized in Table 2.

Assessment of the pulmonary venous pattern on chest radiographs in patients with congenital heart disease and torrential blood flow is not very satisfactory. Occasionally anomalous pulmonary veins can be seen, they are not infrequently associated with atrial septal defects. Anomalous pulmonary venous drainage will be discussed separately. In angiographic studies of congenital heart disease with increased blood flow Goodwin (1958) and Steiner (1958) have been able to demonstrate generalized enlargement of the main pulmonary arteries and the smaller peripheral branches with absence of significant venous distension

Congenital cardiac anomalies associated with torrential pulmonary blood flow are frequently complicated by an increased pulmonary vascular resistance giving rise to very high pulmonary artery pressure; the mechanism and haemodynamics of this complication are fully discussed in Chapters 4 and 9 and the pathological features demonstrated in Chapter 6.

THE RADIOLOGICAL FEATURES OF PULMONARY HYPERTENSION DUE TO INCREASED RESISTANCE

As already stated, this group can be divided into·

(1) Conditions which are associated with increased pre-capillary pulmonary resistance producing a radiological pattern of arterial hypertension.
(2) Conditions associated with increased post-capillary resistance responsible for a radiological pattern of pulmonary venous hypertension.

(A) Causes of Pre-capillary Pulmonary Hypertension (Arterial Hypertension)

(a) Passive secondary to post-capillary hypertension

(1) Mitral stenosis.
(2) Left ventricular failure.

(b) Vasoconstrictive

(1) Mitral stenosis.
(2) Congenital heart disease (atrial septal defect, ventricular septal defect and patent ductus arteriosus).
(3) Hypoxia (pulmonary heart disease).

(c) Obliterative

(1) Chronic obliterative lung disease (extensive pulmonary fibrosis and parenchymal lung destruction).
(2) Various types of arteritis (polyarteritis nodosa, lupus erythematosus, rheumatic arteritis, scleroderma).

will become evident. Considerable dilatation of the main pulmonary artery and its branches will be noticed and this will produce a radiological picture of marked pulmonary hyperaemia (Figs. 25a and 25b) (Campbell, 1951; Keats, *et al.*, 1956; Doyle *et. al*, 1957; Steiner, 1958). The right ventricle is enlarged, but the degree of this may vary. On fluoroscopy intrinsic pulsation can be observed in the large main pulmonary arteries and even in the smaller and medium-sized peripheral branches (Campbell, 1951; Goodwin

TABLE 2

INCREASED PULMONARY BLOOD FLOW

Diagnosis	*Heart*	*Main pulmonary arteries*	*Peripheral arteries*	*Pulmonary veins*
Patent ductus Arteriosus and aortic pulmonary defect	L A.+ L.V.+ R.V + (if P S. or P.H T., R.V.++)	+	Normal or +	Normal (?)
Ventricular septal defect	L V + L.A.+ R.V.+ (if P S. or P.H.T, R V.++)	+	Normal or +	Normal (?)
Atrial septal defect	R V ++ R A.+ (if A V. canal, L.A.+ L.V.+)	++	++	Normal (?)

KEY

+ = slight to moderate ++ = marked
L A. = left atrium L V = left ventricle
R A = right atrium R V = right ventricle
P S = pulmonary stenosis P H T = pulmonary hypertension
A V canal = atrioventricular canal

and Steiner, 1955). Individual variations may be noticed particularly in the size of the main pulmonary arteries. Patients with atrial or ventricular septal defect have usually the largest main pulmonary arteries. These are less prominent in patients with persistent ductus arteriosus or aortic pulmonary communications The degree of intrinsic pulsation and of pulmonary plethora varies considerably and is largely dependent on the size of the shunt. Exceptions, however, do occur. Evans and Short (1958) reported a case with a defect of the aortic pulmonary septum who, on fluoroscopy, exhibited considerable pulmonary artery dilatation, but intrinsic pulsation was absent. The radiological features

TABLE 4

PRECAPILLARY RESISTANCE

Diagnosis	*Heart*	*Main pulmonary artery*	*Small peripheral arteries*	*Pulmonary veins*
Mitral stenosis	L.A.+ or ++	++	Upper zones normal Lower zones narrowed	Upper zones normal or + Lower zones narrowed
Congenital heart disease, "Eisenmenger reaction":				
Atrial septal defect	R.V.++ R.A.+	++	Uniformly narrowed	Normal
Ventricular septal defect	L.V.+ L A + R.V ++	++	"	"
Patent ductus arteriosus	L.V + L A.+ R.V +	+	"	"
Pulmonary heart disease, hypoxic and embolic	R V.+ R.A. normal or +	+	Normal or constricted	Normal
Various types of pulmonary arteritis	R.V.+	+	Constricted	Normal
Idiopathic pulmonary hypertension	R V.+ R A. normal or +	+	Constricted	Normal

CONGENITAL HEART DISEASE

(1) Atrial septal defect.
(2) Ventricular septal defect.
(3) Patent ductus arteriosus.
(4) Aorto-pulmonary defect.

The radiological pattern of the lung vessels due to increased pulmonary blood flow in this group has already been discussed before. As explained in Chapters 4 and 9, a fairly

(3) Embolic (packed pulmonary emboli, including malignant disease).
(4) Atherosclerosis with occlusion.
(5) Congenital heart disease (atrial septal defect, ventricular septal defect and patent ductus arteriosus).

(B) The Causes of Post-capillary Pulmonary Hypertension (Venous Hypertension)

(a) Obstruction of the pulmonary venous flow at left ventricular, left atrial or pulmonary venous level

(1) Mitral valve disease.
(2) Left atrial tumour or thrombus.
(3) Pulmonary venous thrombosis.
(4) Left ventricular failure.

(b) Constrictive pericarditis

The radiological features visible on chest radiographs in patients with a postcapillary hypertension are listed in Table 3 and in patients with [illegible] Table 4. Since the same conditions associated with pulm[illegible] groups of increased precapillary and postcapillary [illegible] pulmonary arterial and pulmonary venous hypertension may be present simultaneously. To avoid confusion and at the risk of slight repetition it is proposed to discuss separately the radiological appearances of the various conditions listed.

TABLE 3

POSTCAPILLARY RESISTANCE

Diagnosis	*Heart*	*Main pulmonary artery*	*Small peripheral arteries*	*Pulmonary veins*
Mitral stenosis	L A.+ or + + R.V.+ or + +	+	Upper zones normal Lower zones narrowed	Upper zones normal or + Lower zones narrowed
Left atrial thrombus or tumour	L A.+ R.V.+	Normal or +	Normal or +	Normal or +
Left ventricular failure	L V.+ L.A.+ if failure R.A.+ (occasionally)	Normal or +	Normal or +	Normal or +

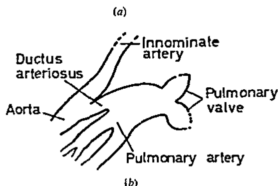
SPECIAL FEATURES OF INDIVIDUAL CONDITIONS WITH A LARGE SHUNT COMPLICATED BY A HIGH PULMONARY VASCULAR RESISTANCE

Patent Ductus Arteriosus

A separate rounded shadow is occasionally seen overlying the aortic arch, probably produced by the ductus (Wood, 1958). The same author also mentions calcification which may be visible radiographically in the ductus. Main pulmonary artery enlargement can be



(a)



(b)

FIG 27 (a and b) Retrograde aortogram lateral projection Baby aged 6 weeks Ventricular septal defect complicated by persistent ductus arteriosus The ductus is clearly demonstrated

marked. The left main pulmonary artery is more frequently dilated than the right; in Wood's (1958) series of patients the right main pulmonary artery was dilated only in ten per cent of cases.

The radiological demonstration of the ductus is best achieved by selective angiography. If the flow in the duct is from the aorta to the pulmonary artery, dilution of contrast material in the pulmonary artery in the diastolic phase will be noticed on the angiographic films early in the examination. On the later films re-opacification of the pulmonary artery from the aorta is occasionally seen. If the flow is reversed, contrast material will be noticed to outline the aorta from the duct early on in the examination.

high proportion of cases of pulmonary hypertension due to increased blood flow will be complicated by high precapillary resistance, producing a pattern of pulmonary arterial hypertension This is signified by marked dilatation of the main pulmonary artery and its main branches and by considerable uniform narrowing of the smaller peripheral vessels (Fig. 26) (Keats *et al.*, 1956, Doyle *et al.*, 1957; Wood, 1958; Evans and Short, 1958). The narrowing of the smaller peripheral pulmonary artery branches is very striking and is responsible for the picture of marked peripheral pulmonary oligaemia which is in direct contrast to the peripheral hyperaemia seen in the patient with big shunts and torrential blood flow and no peripheral resistance. The appearances of the narrowed peripheral vessels on plain X-ray films and angiocardiographic studies have been confirmed in post-mortem angiographic examinations by Evans and Short (1957) and by



FIG 26 5-ft. P A. chest film of a female patient Atrial septal defect with greatly increased precapillary pulmonary resistance Gross dilatation of the main pulmonary artery and its main branches Marked peripheral pulmonary oligaemia

Harrison (1958). On fluoroscopy too, there is a difference between the torrential-flow group and the high-resistance group. In the latter marked intrinsic pulsation of the main distended pulmonary arteries can be observed whereas the smaller peripheral vessels do not show this, indicating a diminution of flow and higher peripheral resistances (Doyle *et al.*, 1957). Accurate correlation of the pulmonary artery pressures with assessment of the main pulmonary artery size is not very satisfactory (Keats *et al*, 1956; Doyle *et al*, 1957), but marked constriction of the smaller peripheral vessels always indicates considerable elevation of the pulmonary artery pressure and a high resistance. *(Steiner, 1958).* The greatest enlargement of the main pulmonary arteries is seen in atrial septal defect and [illegible] 1951; Evans and Short, 1958) Enlargement of cardiac [illegible] ose with a large flow (see

PULMONARY HEART DISEASE

The aetiological haemodynamic features of pulmonary hypertension in cor pulmonale are discussed in Chapters 11 and 12. Wood (1952) classifies pulmonary heart disease as acute, subacute or chronic. The acute and subacute types are usually due to massive pulmonary embolism.

Of radiological importance is the chronic group. This can be obstructive, where small pulmonary arteries and arterioles are blocked by repeated showers of emboli, or due to pulmonary arteritis or malignant disease; it can be hypoxic when pulmonary disease interferes with normal lung function. In this group are included conditions such as chronic bronchitis and emphysema, pneumoconiosis, less commonly pulmonary tuberculosis, various forms of pulmonary fibrosis, scleroderma and sarcoidosis. Severe deformity of the thoracic cage due to marked kyphoscoliosis must also be considered



FIG 28 A P tomogram right lung Male patient with severe pulmonary emphysema The pul-

Hypoxic Pulmonary Heart Disease

In the so-called hypoxic type of pulmonary heart disease two main factors are probably responsible for the elevation of the pulmonary artery pressure and the subsequent radiological changes:

(1) Pulmonary vasoconstriction due to hypoxia.
(2) The obliterative factor leading to strangulation of the pulmonary vascular bed (Wood, 1958).

The pulmonary vascular pattern in this group is often overshadowed by the underlying lung pathology. Clearly visible is dilatation of the main pulmonary artery and its main branches with prominence of the hilar shadows. On fluoroscopy intrinsic pulsation can

To outline the anatomy accurately angiography should be carried out in two planes simultaneously. There are instances when it will be necessary to establish the diagnosis of a patent arteriosus ductus without doubt. This is of particular importance in small infants where a ductus complicates a ventricular septal defect and where definitive surgery is contemplated. In these cases retrograde aortography is the method of choice since filling of the duct from the aorta can clearly be shown and at the same time the accurate anatomy of the aortic arch will also be defined (Figs. 27a and b) (Cleland *et al.*, 1958).

Aorto-pulmonary Septal Defect

From a radiological point of view this defect is best diagnosed by retrograde aortography when contrast medium will be seen to enter the pulmonary artery from the aorta just above the aortic cusps. Since surgery may be considered in the treatment of some of these patients, the angiographic method of examination is important, and should be carried out in two planes to provide adequate anatomical information.

Ventricular Septal Defect

As already stated before, enlargement of the main pulmonary artery may be marked and the left main pulmonary artery is usually larger than the right. In Wood's (1958) series only six per cent of cases showed significant dilatation of the right main pulmonary artery. Left-sided cardiac enlargement may help to distinguish the ventricular septal defect from the atrial septal defect where the right side is correspondingly dilated. In ventricular septal defects and also atrial septal defects in infants, pulmonary lesions, such as lobar or segmental atelectasis with repeated pulmonary infection are frequently seen (Krabrenhoft and Evans, 1954)

Atrial Septal Defect

Not only is there considerable dilatation of the main pulmonary artery but also of its main branches. In Wood's (1958) series the right main pulmonary artery was grossly dilated in 60 per cent of the cases. The aortic knuckle may appear small and overshadowed by the very distended pulmonary artery and its left main branch The association of a very large heart with pulmonary hypertension in a child should arouse the suspicion of a common atrioventricular canal (see Chapter 7).

Acute pulmonary oedema or chronic interstitial pulmonary oedema is very rare in atrial septal defects, ventricular septal defects and ductus arteriosus so that the radiological features of pulmonary oedema and the features of a raised pulmonary venous pressure are seen only infrequently. Dexter, in 1956, was able to show that the pulmonary venous pressure in 14 patients out of 60 with atrial septal defects was appreciably raised, and concluded that mitral lesions might have been responsible for this. The Lutembacher complex where mitral stenosis is more marked is an obvious cause for a raised left atrial and pulmonary venous pressure (Grainger, 1958). Basal septal lines in the peripheral lung fields are a characteristic radiological finding in patients with a raised pulmonary venous pressure. This will be further discussed under the section "post capillary or pulmonary venous hypertension".

PULMONARY HEART DISEASE

The aetiological haemodynamic features of pulmonary hypertension in cor pulmonale are discussed in Chapters 11 and 12. Wood (1952) classifies pulmonary heart disease as acute, subacute or chronic. The acute and subacute types are usually due to massive pulmonary embolism.

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FIG 28 A P tomogram right lung Male patient with severe pulmonary emphysema The pulmonary arteries are dilated and so is the right upper lobe artery. The upper lobe peripheral arteries are of normal calibre but crowded together Mid-zone and lower zone arteries [illegible]

Hypoxic Pulmonary Heart Disease

In the so-called hypoxic type of pulmonary heart disease two main factors are probably responsible for the elevation of the pulmonary artery pressure and the subsequent radiological changes:

(1) Pulmonary vasoconstriction due to hypoxia.
(2) The obliterative factor leading to strangulation of the pulmonary vascular bed (Wood, 1958).

The pulmonary vascular pattern in this group is often overshadowed by the underlying lung pathology. Clearly visible is dilatation of the main pulmonary artery and its main branches with prominence of the hilar shadows. On fluoroscopy intrinsic pulsation can

be seen in the main pulmonary vessels. The smaller peripheral arteries, if distinguishable, are either normal or slightly narrowed. When there is marked emphysema the smaller pulmonary arteries appear considerably narrowed, elongated and stretched; or they may be completely absent where there is bullous emphysema (Fig. 28) (Lodge, 1948; Simon.





FIG 29a 6-ft P A chest film. Middle-aged



FIG 29b 6-ft P A chest film Same patient as Fig 29a two weeks later after acute exacerbation The heart shadow has decreased in size, also diminution in size of the main pulmonary artery and its main branches

1956). Variations in heart size are particularly noticeable in cor pulmonale, it may be of normal size or it may appear relatively small as in emphysema when the diaphragm is low in position and the heart rotated anticlockwise. Alternatively, the right ventricle may be markedly enlarged together with extensive dilatation of the main pulmonary arteries This is most noticeable in an acute exacerbation of the disease. As the patient's condition improves and the pulmonary artery pressure drops to normal levels, regression in heart and pulmonary artery size will be noted (Figs. 29a and b) (Mounsey *et al*, 1952) Another valuable radiological sign is some degree of prominence of the vena cava and azygos vein, which may be visible on the P.A. chest film along the right upper mediastinal border. The azygos vein can be seen as an oval or round opacity just above the right hilum. These signs have been described by Fleischner (1957) who also observed that the transverse diameter of the azygos vein can be accurately measured and appears to fluctuate in size concomitantly with the patient's condition.

Obstructive Pulmonary Heart Disease

In this type of pulmonary heart disease, irrespective of its cause, dilatation of the main pulmonary artery and its main branches can be very marked and this is associated with

As in hypoxic pulmonary ... associated finding. Since the pulmonary artery pressure can be very high in this ... pulsation is often marked and clearly visible in the main pulmonary arteries whereas in the smaller peripheral vessels it is completely absent. Gross dilatation of one large pulmonary ... main lobar artery, with segmental narrowing of its peripheral branches may be see ... (Figs. 31a and b) Ball *et al.*, 1956). ... ndary to peripheral thrombosis, or is due to primary ... such as

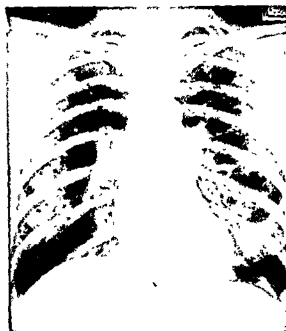


FIG. 30 6-ft P A chest film middle-aged male patient. Long history of thrombo-embolic disease Packed pulmonary emboli Main pulmonary artery and main branches are dilated Smaller peripheral branches relatively narrow, lung fields clear.

mitral stenosis, was the commonest single cause and occurred in six cases out of 53 ... by Ball *et al.* (1956) In some cases calcification within the thrombus at the edge ... as a dense linear opacity ... in this ... ry with sudden cessation of pulsation at the ... ation is absent over the distended artery it indicates further spread of clot into that section of the ...

... to the appearances of the ... without infarction. Varia- ... which there ... A more

be seen in the main pulmonary vessels. The smaller peripheral arteries, if distinguishable, are either normal or slightly narrowed. When there is marked emphysema the smaller pulmonary arteries appear considerably narrowed, elongated and stretched; or they may be completely absent where there is bullous emphysema (Fig. 28) (Lodge, 1948; Simon, 1956). Variations in heart size are particularly noticeable in cor pulmonale, it may be of normal size or it may appear relatively small as in emphysema when the diaphragm is low in position and the heart rotated anticlockwise. Alternatively, the right ventricle may be markedly enlarged together with extensive dilatation of the main pulmonary arteries This is most noticeable in an acute exacerbation of the disease As the patient's condition improves and the pulmonary artery pressure drops to normal levels, regression in heart and pulmonary artery size will be noted (Figs. 29a and b) (Mounsey *et al.*, 1952). Another valuable radiological sign is some degree of prominence of the vena cava and azygos vein, which may be visible on the P.A. chest film along the right upper mediastinal border. The azygos vein can be seen as an oval or round opacity just above the right hilum. These signs have been described by Fleischner (1957) who also observed that the transverse diameter of the azygos vein can be accurately measured and appears to fluctuate in size concomitantly with the patient's condition.





FIG 29a 6-ft P A chest film Middle-aged female patient, long history of bronchitis and emphysema, pulmonary heart disease. The main pulmonary artery and its main branches are dilated, also right ventricular enlargement

FIG 29b 6-ft. P A. chest film Same patient as Fig 29a two weeks later after acute exacerbation The heart shadow has decreased in size, also diminution in size of the main pulmonary artery and its main branches

Obstructive Pulmonary Heart Disease

In this type of pulmonary heart disease, irrespective of its cause, dilatation of the main pulmonary artery and its main branches can be very marked and this is associated with

Idiopathic Pulmonary Hypertension

This is a rare condition and occurs mainly in young women (Evans *et al.*, 1957). Marked dilatation of the main pulmonary artery and its main branches with right ven-



FIG 32 6-ft. P A chest film—middle-aged man

due to an infarct.

tricular enlargement will be noticed radiologically. Associated with this there is considerable narrowing of all smaller peripheral vessels producing a very convincing picture of

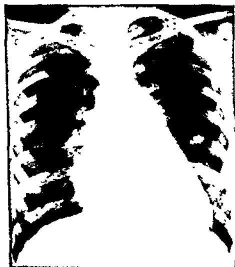


FIG 33 6-ft P A chest film Young female patient

monary artery markedly dilated, smaller peripheral vessels narrowed Considerable pulmonary oligaemia

peripheral pulmonary oligaemia (Fig 33) (Steiner, 1958). On fluoroscopy intrinsic pulsation of the main dilated vessels is very obvious whereas in the smaller peripheral

detailed description of the radiological appearances of pulmonary infarction will follow later.

In some patients with peripheral embolic disease, recurrent showers of small emboli may produce obstructive lesions in the smaller peripheral arteries (Fig. 30) (Davison *et al.*, 1956). In some tropical countries, particularly Egypt, bilharzial eggs can reach the smaller lung arteries, producing a similar obstructive lesion (Girgis, 1952). This trend of events will also produce a radiological picture of obstructive cor pulmonale very similar to the



FIG. 31a. 6-ft P A chest film Patient with thrombo-embolic pulmonary hypertension Right ventricular pressure 85/4 mm Hg and the cardiac output 3 3 l. min Thrombosis of



FIG 31b Same patient as Fig 31a Venous

...s already

...ing fields

Rarely pulmonary hypertension may complicate a collagen disease such as polyarteritis (Fig. 32) or possibly rheumatoid arteritis (Wade and Ball, 1957), scleroderma (Evans, 1959), dermatomyositis (Caldwell and Aitchison, 1956) and Lupus erythematosus. In this group too, in addition to the abnormal vascular pattern of cor pulmonale, pulmonary parenchymal lesions can be seen such as fine mottling in polyarteritis due to small infarcts or haemorrhages (Scadding, 1956), or there may be extensive linear fibrosis with widespread mottling as in Lupus erythematosus and scleroderma (Lodge, 1956).

Idiopathic Pulmonary Hypertension

This is a rare condition and occurs mainly in young women (Evans *et al.*, 1957). Marked dilatation of the main pulmonary artery and its main branches with right ventricular enlargement will be noticed radiologically. Associated with this there is considerable narrowing of all smaller peripheral vessels producing a very convincing picture of peripheral pulmonary oligaemia (Fig 33) (Steiner, 1958). On fluoroscopy intrinsic pulsation of the main dilated vessels is very obvious whereas in the smaller peripheral



FIG 32 6-ft P.A. chest film—middle-aged man with Polyarteritis Nodosa Main pulmonary artery and main branches dilated. Scattered throughout the periphery of the left lung multiple small shadows due to exudates, a larger segmental lesion in the right mid-zone due to an infarct

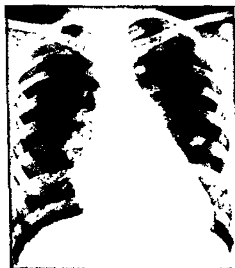


FIG. 33 6-ft P A chest film Young female patient with idiopathic pulmonary hypertension. Pulmonary artery pressure 110/40 mm Hg Considerable right ventricular enlargement. Slight right atrial enlargement Main pulmonary artery markedly dilated, smaller peripheral vessels narrowed Considerable pulmonary oligaemia

branches it is completely absent. The radiological differentiation of idiopathic pulmonary hypertension and the various forms of pulmonary arteritis due to collagen disease depend largely on the absence of parenchymal shadows which are common in collagen disorders.

Methods of Radiological Investigation

In the study of pulmonary vasculature in pulmonary hypertension associated with cor pulmonale, plain chest radiography is all that is required in most cases. If there is considerable parenchymal disease obscuring pulmonary vessels, tomography will be of help in outlining the pulmonary arteries more easily as well as in demonstrating the parenchymal lesions If there is massive pulmonary artery thrombosis, venous angiography is the method of choice to demonstrate the vascular block. Selective pulmonary arteriography should not be used in these patients, since catheterization of the pulmonary artery with subsequent contrast injection may dislodge blood clot and lead to further embolization. In the collagen disorders, and particularly primary pulmonary hypertension, angiocardiography is dangerous.

PULMONARY INFARCTION

Pulmonary embolism without infarction has been discussed before. Pulmonary infarction can be present pathologically without the production of a shadow in the lungs (Hampton and Castleman, 1940).

In only about two-thirds of patients with pulmonary infarction can one detect radiological abnormalities in chest radiographs which are directly attributable to a pulmonary infarct.

A large variety of different shadows can appear at varying times after infarction and it is important to be familiar with these divergent patterns and to look for specific lesions The radiological diagnosis can be difficult and at times impossible without clinical correlation.

The Radiological Appearances which may be met with in Pulmonary Infarction

(1) Consolidation.
(2) Slight loss of translucency (without well-defined borders).
(3) A linear shadow
(4) Triangular shadows (rare).
(5) Segmental collapse.
(6) Pulmonary scarring.

[illegible] ry infarction [illegible] ity although [illegible] lidated area [illegible] frequently lies at the edge of the lung under the parietal pleura or along the fissures (Hampton and Castleman, 1940; Fleischner, 1958). Thus in some projections the shadow will appear dense, whereas in another projection it may only produce a faint opacity. Multiple shadows are not infrequent; Short (1951) records a 43 per cent incidence in his series. Infarcts are more common in the right than in the left lung, the proportions are

about two to one and more frequent at the bases than in the upper and mid-zones (Short, 1951). Linear shadows can appear during the stage of resolution and are probably due to small areas of segmental atelectasis. Similarly more extensive pulmonary atelectasis which is mainly basal can develop during the stage of resolution. Linear scars are not an uncommon sequel to massive infarcts and appear as a dense linear network, or single dense linear shadows in the area of the original lesion These scars are indistinguishable from those produced by inflammatory processes such as lung abscesses or pneumonia.

Pleural effusion. Pleural effusions are a common occurrence, small collections can be seen in about half the cases, they may be basal or interlobar. The effusions can persist for long periods, even months, and after reabsorption of the fluid, pleural thickening or pleural adhesions persist.

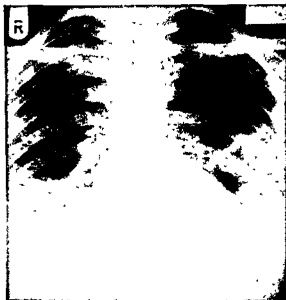


FIG 34 6-ft P A chest film Male patient with recent pulmonary infarction. Both diaphragmatic domes elevated segmental areas of consolidation at both bases due to infarcts Small effusion at the left base

Diaphragmatic elevation. Diaphragmatic elevation on the side of the lesion with restricted movement on fluoroscopy was reported in 35 per cent of the cases (Short, 1951); this was usually associated with lower lobe infarction After resolution of the infarct the diaphragm returned to a normal position.

Time relationship of infarction to radiographic shadows. Radiographic shadows can appear within hours after pulmonary infarction, a small pleural reaction or slight clouding of the lung may be the earliest sign, or there may be distension of a major pulmonary artery branch leading towards the infarcted segment of the lung (Fleischner, 1958), which may present as an avascular area. These signs can then be followed by extensive pulmonary consolidation, diaphragmatic elevation or massive effusions which may mask the pulmonary infarcts. The rate of resolution is also variable. Hampton and Castleman (1940) reported rapid clearing within two to four days On the other hand resolution of the shadow may be prolonged for weeks and even months (Scherf and Boyd, 1948; Short, 1951).

Differential diagnosis. This can be difficult radiologically since the shadows produced by pulmonary infarcts are so variable and are very similar to shadows produced by a variety of other conditions.

1. *Lobar pneumonia.* The differential diagnosis is largely a clinical one. Pneumonic consolidation is usually more extensive than that seen by infarction. Diaphragmatic elevation is more marked after infarction than pneumonic consolidation.

2. *Pleural effusion.* If the infarct is basal and in the costophrenic angle, the differentiation from fluid depends on the contour of the shadow; fluid presents with a concave upper border whereas an infarct has an irregular, humped or more convex upper border (Short, 1951). A lateral or oblique film may be of help to localize the segmental area of consolidation.

3. *Pulmonary collapse.* This does not occur in the early stage of infarction, but if the other signs such as marked diaphragmatic elevation and pleural effusions are also present it will suggest infarction

MITRAL VALVE DISEASE

Specific lung lesions have been recognized for many years and have been associated with disordered pulmonary function. In 1936 Parker and Weiss were able to demonstrate pathological changes in the alveolar walls, in the small pulmonary arteries and arterioles in patients with severe mitral stenosis. The alveolar walls showed thickening of the basement membrane and there appeared to be interstitial oedema of the interlobular septa. The lumen of the pulmonary arterioles was narrowed by muscular hypertrophy frequently associated with scarring and occasionally atheroma. Similar changes have been reported by Larrabee *et al.* (1949); Bayliss *et al.* (1950); Evans and Short (1957) and Harrison (1958) The pathological detail is described in Chapter 6

Pulmonary arterial and venous hypertension is almost invariably a complication of severe mitral stenosis and for discussion of the clinical and physiological background of the problem the reader is referred to Chapter 8.

The Radiological Appearance in the Lungs in Mitral Heart Disease

Three main lesions can be described.

(1) Changes in the pulmonary vascular pattern affecting the pulmonary arteries and veins.
(2) Pulmonary oedema which can be either chronic and interstitial or acute and alveolar.
(3) Fine pulmonary nodulation due to haemosiderosis and coarser and very dense nodulation due to pulmonary ossification.

The Radiological Appearances of the Pulmonary Vessels in Mitral Disease

These can be divided into alterations of (1) the vascular pattern due to arterial hypertension, and (2) the vascular pattern due to venous hypertension.

The pulmonary arteries. Alterations in the radiological pulmonary vascular pattern in mitral heart disease occurs due to a rise in the pulmonary arterial pressure secondary to elevated pulmonary venous pressure. These vascular changes were first observed radiographically by Goodwin *et al.* (1952) and by Actis-Dato *et al* (1952) The first observations were made on angiographic studies of the pulmonary arteries. Subsequently a large number of papers have appeared in the literature confirming these observations (Steiner and Goodwin, 1954; Bülow *et al.*, 1955; Bolt *et al.*, 1957) The angiographic appearances were compared with those seen on chest radiographs by Davies *et al.* (1953), who found

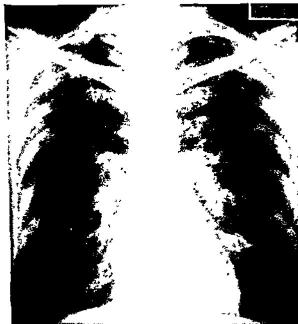


Fig 35a 6-ft P A chest film Patient with mitral stenosis, normal pulmonary artery and pulmonary capillary [illegible]



Fig 35b Selective pulmonary arteriogram of the left lung in a patient with mitral stenosis and insignificant pulmonary hypertension Pulmonary arteries are of normal calibre throughout the lung.

a good correlation, as did Fleischner and Sagall (1955), Van Epps (1958) and Boyd *et al* (1958) Although Bülow *et al.* (1955) also found a good correlation, these authors felt that the interpretation of the vascular changes on chest radiographs was at times difficult.

When the pulmonary arterial pattern in patients with mitral stenosis is carefully studied on chest radiographs, or even better on contrast studies such as pulmonary arteriograms, it will be noted that in patients with a normal arterial pressure the appearance of the pulmonary vascular pattern is normal. The main pulmonary artery and its main branches are not significantly enlarged and the smaller divisional arterial branches well out in the peripheral lung fields divide equally and regularly and are of a calibre proportional to the

larger branches from which they arise (Figs. 35a and 35b). When the systolic arterial pressure rises to a level of about 60–70 mm Hg very marked dilatation of the main pulmonary artery will be noted, whereas the smaller peripheral branches appear considerably narrowed and attentuated; they may even appear truncated, irregular and tortuous, with ill-defined borders. These changes in the pulmonary artery size and contour occur in the third and fourth divisional branches beyond the hilum and are most marked in the lower

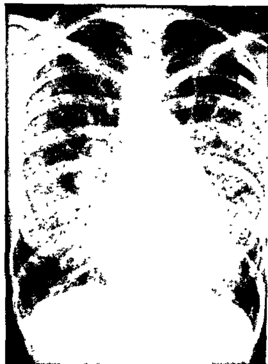


FIG 36a 6-ft P A chest film Young female patient with mitral stenosis and severe pulmonary hypertension 115/60 mm Hg Main pulmonary artery is considerably dilated, as well as main branches Peripheral upper lobe arteries of normal calibre, peripheral upper lobe arteries of normal calibre, peripheral mid-zone and lower lobe arteries narrowed and irregular "Abnormal Pulmonary Arterial Pattern" Septal lines at both bases due to interstitial pulmonary oedema



FIG 36b Selective pulmonary arteriogram—female patient with severe pulmonary hypertension 100/54 mm Hg Cardiac output 4 2 l/min Marked dilatation of main left pulmonary artery Vascular pattern of the upper zone normal Considerable narrowing of the smaller segmental arteries of the mid and lower zones

and mid zones whereas in the upper zones of the lungs the arterial vascular pattern is normal (Figs 36a and b) (Doyle *et al*, 1957). These authors also discussed in their paper a possible mechanism for this discrepancy (see Chapter 8). The pulmonary venous pressure and left atrial pressure in severe mitral stenosis is considerably raised. If the hydrostatic pressure, which in the erect posture is higher at the base of the lungs than at the apices, is added to the already elevated venous pressure a critical level will be reached. This may excite arterial constriction in the lower mid zones of the lung, diminish pul-

monary flow and prevent oedema The effect of this on the radiographic appearance of pulmonary oedema will be discussed later.

Peripheral arterial constriction in mitral stenosis is therefore very different in distribution from that seen in congenital heart disease with high peripheral resistance. As mentioned before in the congenital group narrowing of the small peripheral arteries is uniform throughout the lung, the selective arterial response not being involved since the venous pressure is normal or only insignificantly raised. No suggestions for the mechanism of this generalized arterial constriction is offered by Doyle *et al* (1957) but various pathological explanations, such as persistence of a foetal anatomy of the pulmonary vascular tree has been suggested (see Chapters 6, 9).



FIG 37 Same patient as Fig 36a Venous phase of selective pulmonary arteriogram Left upper lobe veins dilated. Lower lobe veins small and irregular

When the pulmonary arterial pressure is only moderately elevated below 60 mm. of mercury systolic, the vascular changes just described also occur but are less marked and only confined to the bases and therefore not so clearly distinguishable on chest radiographs.

Enlargement of the main pulmonary artery was originally described by Zdansky (1929, 1930) and put into perspective in mitral heart disease by Parkinson (1949). Accurate correlation of main pulmonary artery size and the pulmonary artery pressure is not altogether satisfactory (Jacobson *et al.*, 1957) A significantly elevated pulmonary arterial

pressure, however, is usually associated with marked dilatation of the main pulmonary artery, whereas a normal pressure will be associated with no dilatation (Davies *et al*, 1953).

Radiographically it is impossible to distinguish arterial narrowing due to vasoconstriction and narrowing due to secondary arterial disease such as atheroma or thrombosis (see Chapter 6) The only significant sign of atheroma may be visible calcification which is rare and when present will appear as linear calcification along the vessel margin—similar to that described before under pulmonary arterial thrombosis.

The arterial changes are by no means static. They will progress as mitral stenosis increases in severity but regression to a normal pattern, even after successful valvotomy, is not very common (Goodwin *et al.*, 1955; McAffee and Biondetti, 1957).

The vascular appearances offer a most valuable index in establishing radiologically the level of the pulmonary arterial pressures as well as assessing the progress of the disease.

The radiological appearance of the pulmonary veins. There is some difficulty is assessing the pulmonary venous pattern on chest radiography as already stated in the opening section of this chapter In patients with a normal or only slightly raised pulmonary venous pressure, the appearance of the pulmonary veins on conventional chest films is usually quite normal (Steinbach *et al*, 1955). These authors also observed that in some cases of mitral stenosis the pulmonary veins appear constricted. Simon (1958) described considerable venous dilatation of the upper lobe veins in tight mitral stenosis visible on chest radiographs.

If the pulmonary venous pressure is markedly elevated, Steiner (1958) has shown on selective angiographic studies that at pulmonary capillary pressure level from 35–40 mm. Hg the upper lobe veins appear dilated whereas the lower lobe veins are either of normal calibre or narrowed (Fig 37). At pressure levels between 15–25 mm Hg the upper lobe veins appear dilated or normal in some cases, whereas the lower and mid-zone veins are of normal calibre In the normal pressure range the venous pattern is normal. Similar observations in tight mitral stenosis with a high pulmonary venous pressure were reported by Arvidsson and Ödman (1957).

Pulmonary Oedema in Mitral Heart Disease

A detailed discussion of the radiological pattern in pulmonary oedema will follow later in this chapter in a separate section. At this point the appearance of pulmonary oedema only in relationship to mitral heart disease will be described

1. *Acute pulmonary oedema.* This complication can occur in mitral stenosis. Wood (1954) reported it in eight per cent of his patients with significant mitral stenosis. The radiological appearances of acute pulmonary oedema are described later (Figs. 38a and b)

2. *Interstitial pulmonary oedema* This type of pulmonary oedema is seen much more frequently in mitral heart disease than acute pulmonary oedema and produces distinct radiological signs indicating a raised pulmonary venous pressure.

The most important signs are fine dense and well-defined interlobar septal lines which were first described by Kerley (1933) These septal lines are best seen at the edge of the lungs, at the bases, but they can also extend into the mid-zones. They vary in length from 1–3 cm (Fleischner and Reiner, 1954). Occasionally they are accompanied by longer

straight or slightly curved dense lines which run *from the periphery of the lung to the hila*; they too represent distended interlobular septa (Fig. 39).

by a number of workers provided con- of the lines is due to distension of the ly due to distended pulmonary lymphatics, although dilated lymphatics may be found within the septa (Fleischner and Reiner, 1954; Gough, 1955; Grainger and Hearn, 1955; Short, 1955, Grainger, 1958) Several observers have also correlated the appearance of the septal lines with pulmonary venous pressure levels and have all found a more or less critical level of 20–25 mm Hg (pulmonary



FIG 38a A P Ward Unit chest film of a middle-aged woman with mitral stenosis Acute pulmonary oedema Widespread consolidation throughout the right lung and some consolidation at the left base



FIG 38b Same patient one day later Oedema has cleared Pulmonary arterial changes in the lungs indicating elevated pulmonary artery pressure persist Septal lines at the bases are partly obscured by small transudates

capillary pressure) below which septal lines are rarely seen (Carmichael *et al*, 1954; Grainger and Hearn, 1955; Levin, 1955; Grainger, 1958).

Successful valvotomy or adequate medical treatment, when followed by a drop in the pulmonary venous pressure to levels below 20 mm Hg will often lead to a disappearance of interstitial oedema and disappearance of septal lines (Grainger and Hearn, 1955); but even after adequate therapy the septal lines may persist. This was shown by Fleischner and Reiner (1954), who demonstrated extensive haemosiderin accumulations within the septa and thought it to be the cause of this persistence. Septal lines may often occur due to interstitial pulmonary oedema in other conditions. For example their presence in some cases of atrial septal defects has already been mentioned; their occurrence in left ventricular failure will be discussed later. *Lymphatic obstruction can be another cause of the presence*

of septal lines as, for example, in mediastinal glandular enlargement due to malignan disease and associated lymphangitis carcinomatosa or reticulosis. Septal lines hav occasionally been present in pneumoconiosis (Gough, 1955)

Subserous accumulations of oedema fluid, which can extend *into the interlobar fissure* may lead to pleural thickening, are yet another manifestation of chronic interstitial pul monary oedema. This fluid retention will give rise to a slight loss of translucency in th affected areas of the lung and may be one of the causes for a general haziness of the lun fields, particularly in the lower zones Another cause for haziness is probably a widesprea



FIG 39 Localized views of the right mid and lower zone of patient with mitral stenosis, severe pulmonary arterial and pulmonary

interlobular oedema extending into the more central areas of the lung, and is one of the reasons why interpretation of the pulmonary vascular markings in the lower zones may be difficult (Short, 1955; Bulow *et al.*, 1955)

Synthesis of Radiological Signs of Pulmonary Arterial and Venous Hypertension in Mitral Stenosis

Pulmonary arterial hypertension:

(1) Enlargement of the main pulmonary artery.
(2) Normal peripheral upper lobe arteries, constricted and narrowed lower lobe and mid-zone arteries.

Pulmonary venous hypertension:

(1) Normal or dilated upper lobe veins.
(2) Normal or constricted lower lobe veins.
(3) Septal lines.
(4) Thickened interlobar fissures and haziness of the lower lung fields.

The Heart in Mitral Disease and the Radiological Signs of Pulmonary Hypertension

There is no positive correlation between left atrial size and the degree of pulmonary hypertension (Steiner and Goodwin, 1954) In tight mitral stenosis with a high pulmonary artery pressure and vascular changes in the lung fields, a relatively small left atrium is



FIG 40 6-ft P A. chest film of patient with mitral stenosis and moderate pulmonary hypertension. Fine miliary mottling due to haemosiderosis, particularly in the mid-zones.

usually seen; occasionally however, the atrium can be very large. Some degree of right ventricular enlargement is always seen if there is significant pulmonary hypertension The radiological signs of pulmonary venous hypertension are often present both in mitral stenosis and mitral incompetence Radiological signs of severe pulmonary arterial hypertension are seldom seen in predominant incompetence and suggest predominant stenosis. Patients with predominant mitral stenosis and radiological signs of venous hypertension preoperatively usually do well after successful valvotomy (Grainger and Hearn, 1955) No visible change in the radiological signs of pulmonary venous hypertension after valvotomy usually means an unsuccessful operation or haemosiderin deposits in the septa. A change for the better after operation with gradual recurrence of radiological signs later probably indicates re-stenosis of the valve.

In the presence of significant tricuspid insufficiency the pulmonary vascular changes

due to high venous and arterial pressures can regress considerably, thus a relatively normal appearance of the lung vascular pattern is not unusual in this situation.

Haemosiderosis. In extensive studies of pulmonary haemosiderosis, Scott *et al.* (1947) and Lendrum *et al.* (1950) came to the conclusion that haemosiderosis resulted from multiple interpulmonary haemorrhages which occurred at varicose bronchopulmonary capillary anastomoses which had ruptured into terminal bronchioles. These haemorrhages later on led to an accumulation of haemosiderin within the lung.

Provided the aggregates of haemosiderin are large enough and fairly widespread the radiological pattern of a fine diffuse nodulation can be seen on chest radiographs. The general distribution of the nodules is fairly uniform but they appear more marked in the mid-zones and lower zones than towards the apices (Fig. 40) Minor changes may be so indistinct that a definite diagnosis on the X-ray film cannot be made.

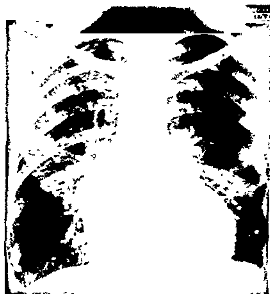


FIG 41 6-ft. P A. chest film of a patient with mitral stenosis Dense nodules scattered throughout the lung fields due to extensive pulmonary ossification in the mid and lower zones

The incidence of radiologically recognizable haemosiderosis in mitral heart disease varies from 10–15 per cent (Goodwin *et al.*, 1955) Haemosiderosis is usually associated with some degree of pulmonary hypertension (Steiner *et al*, 1954, Goodwin *et al.*, 1955). Wood, however, in 1954 could find no such a correlation.

In the differential diagnosis of haemosiderosis other pulmonary conditions producing a fine nodular pattern must be considered such as miliary tuberculosis, some forms of [illegible] and idiopathic haemosiderosis. The association of an enlarged heart of [illegible] will be most probably due to haemo- [illegible] shadows appear on the radiograph they can either remain static or progress over the years, but they occasionally regress (Ellman and Oliver, 1959).

Pulmonary ossification. The first description of a case of pulmonary ossification and appreciation of its association with mitral valve disease was presented by Salinger in 1932. Since then a number of case reports of this unusual manifestation have appeared in the literature (Grishman and Kane, 1945; Elkeles and Glynn, 1946; Kerley, 1951). A detailed

review with a report of another seven cases was published by Whitaker *et al.* (1955) and Fleming and Robinson (1957), who added another eight cases of their own and discussed the aetiology and pathology.

The ossified nodules are usually seen in the lower and mid-zones of the lung in patients with mitral heart disease (Fig. 41) They can appear within a relatively short period—I have seen them develop within a year in one patient. There is good evidence that they occur in patients with tight mitral stenosis associated with elevation of the pulmonary venous and pulmonary atrial pressures (Whitaker *et al.*, 1955; Fleming and Robinson, 1957) Pathologically the nodules are true lamellar bone and probably develop in areas of interstitial pulmonary oedema Since haemosiderosis in some of the cases reported was very slight or absent, the suggestion by Lawson (1949) and Ellman and Gee (1951) that these two conditions are causally related can no longer be accepted.

LEFT ATRIAL TUMOUR AND LEFT ATRIAL BALL VALVE THROMBUS

In these unusual conditions significant radiological findings will only be observed when the thrombus or tumour mass is of sufficient size to obstruct the mitral valve orifice significantly and thus produce a rise in the left atrial and in the pulmonary venous pressures. In left atrial tumours the appearances of the heart shadow (Steinberg *et al.*, 1953) and also to some extent the vascular appearances in the lungs (Steiner, 1958) are very similar to those seen in mitral stenosis. The degree of the changes will depend largely on the severity of the mitral valve obstruction and the levels of the left atrial and pulmonary venous pressures. The radiological differentiation between mitral stenosis and left atrial tumour on a plain chest radiograph is impossible and only with the aid of contrast studies, such as angiocardiography, can a tumour or thrombus in the left atrium be demonstrated (Goldberg *et al.*, 1952). A massive thrombus may calcify and thus become visible radiographically.

PULMONARY VENOUS OCCLUSION

This is an exceedingly rare condition and when it occurs there will be radiological evidence of a raised pulmonary venous pressure. In a case reported by Emslie-Smith *et al.* (1955) the distribution of interstitial pulmonary oedema was restricted to the right lung where the pulmonary veins were obliterated by a congenital membranous septum demonstrated at post-mortem, whereas the pulmonary arterial vascular changes were bilateral due to a high peripheral pulmonary resistance associated with a patent ductus arteriosus. Another case reported by Grainger (1958) was of a child with severe interstitial pulmonary oedema of generalized distribution At post-mortem widespread occlusions of smaller pulmonary veins were demonstrated, associated with marked oedema of interlobular septa, distended pulmonary lymphatics and thickened and oedematous alveolar walls.

LEFT VENTRICULAR FAILURE

Left ventricular failure irrespective of its underlying cause can be associated with a distinctive radiological picture. Important causes of left ventricular failure are: hypertension, aortic valve disease and ischaemic heart disease For the clinical background the reader is referred to Chapters 13, 14.

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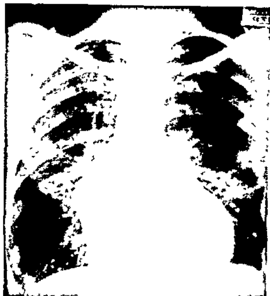


FIG 41. 6-ft. P A chest film of a patient with mitral stenosis Dense nodules scattered throughout the lung fields due to extensive pulmonary ossification in the mid and lower zones.

mid-zones and lower zones than towards the apices (Fig. 40) Minor changes may be so indistinct that a definite diagnosis on the X-ray film cannot be made.

The incidence of radiologically recognizable haemosiderosis in mitral heart disease varies from 10–15 per cent (Goodwin *et al.*, 1955). Haemosiderosis is usually associated with some degree of pulmonary hypertension (Steiner *et al.*, 1954; Goodwin *et al.*, 1955) Wood, however, in 1954 could find no such a correlation.

In the differential diagnosis of haemosiderosis other pulmonary conditions producing a fine nodular pattern must be considered such as miliary tuberculosis, some forms of pneumoconiosis and idiopthic haemosiderosis. The association of an enlarged heart of mitral configuration and miliary mottling of the lung will be most probably due to haemosiderosis. Once haemosiderosis has developed and shadows appear on the radiograph they can either remain static or progress over the years, but they occasionally regress (Ellman and Oliver, 1959).

Pulmonary ossification. The first description of a case of pulmonary ossification and appreciation of its association with mitral valve disease was presented by Salinger in 1932. Since then a number of case reports of this unusual manifestation have appeared in the literature (Grishman and Kane, 1945; Elkeles and Glynn, 1946; Kerley, 1951). A detailed

4. *Enlargement of the main pulmonary arteries and pulmonary veins.* As already mentioned, fullness of the hilar shadows due to vascular distension is frequently noted. On the other hand the assessment of the peripheral vascular pattern in the lung fields is not very satisfactory in left ventricular failure. Dilatation of the main lobar arteries and veins can be seen but there does not appear to be any marked alteration in calibre of the smaller vessels on the chest film, although theoretically narrowing of the lower lobe arteries could well be present.

Lewis *et al* (1953) have reported an elevated pulmonary artery pressure in patients with prolonged and severe left ventricular failure. The levels of the pulmonary artery pressure are not as high as in cases of tight mitral stenosis, nor does pulmonary hypertension persist for a prolonged time. These may be the reasons why peripheral pulmonary vascular changes are not demonstrable radiologically in patients with left ventricular failure. Some vascular hypertrophy of the smaller pulmonary arteries has been demonstrated histologically in patients with left ventricular failure due to hypertension and aortic valve disease by Smith *et al* (1954). These pathological findings further support the evidence of an elevated pulmonary artery pressure in some cases of left ventricular failure.

The radiological signs described are often quite transitory in left ventricular failure which is in contradistinction to mitral stenosis, where steady progression of the vascular lesions is very common Another point of distinction between the two conditions is the frequent association of a bilateral hydrothorax in left ventricular failure This is not common in mitral stenosis where only a small transudate occurs which is often unilateral. The degree of interstitial pulmonary oedema also differs and is much less marked in left ventricular failure than in mitral stenosis.

The Heart in Left Ventricular Failure.

As to be expected left ventricular enlargement is the most striking radiological sign in left ventricular failure. It has been shown by Cobbs *et al.* (1957) that the left atrium can also enlarge and this can readily be demonstrated radiographically. Left atrial enlargement will occur when left ventricular failure is marked or has been present on a number of occasions; thus left atrial enlargement will be visible together with the pulmonary manifestations of chronic interstitial oedema

PULMONARY OEDEMA

(A) *Intra-alveolar.* (*a*) Acute, most commonly due to left ventricular failure in hypertension and in mitral stenosis. (*b*) Subacute, this is uncommon and occurs in left ventricular failure complicated by uraemia, as in acute nephritis, polyarteritis nodosa, malignant hypertension.

(B) *Interstitial*

The radiological features of acute and subacute oedema will be described in this section. The exact mechanism of pulmonary oedema is not fully understood. A number of different factors play a part, for instance, the lymph drainage of the lungs, pulmonary capillary and pulmonary hydrostatic pressure and the capillary permeability (Drinker, 1945; Cameron, 1948; Grainger, 1958) One of the main factors for production of pulmonary oedema due

The radiological appearances can be considered from two aspects:

(1) **Acute heart failure.** This is associated with acute pulmonary oedema and will be dealt with later in a separate section.

(2) **Chronic left heart failure.** This can present in a variety of ways, producing pulmonary changes due to a raised pulmonary venous pressure.

The most striking radiological features in left heart failure of more gradual onset are:

1. *Hilar clouding* This was found by Short (1956) to be the most constant and frequent appearance. *In a high proportion of his patients this author noted fullness of the* hilar shadows with a loss of definition of individual vascular branches (Fig. 42). This



FIG 42 6-ft P A chest film middle-aged female patient left ventricular failure due to aortic valve disease Effusion at the left base The main pulmonary artery is dilated and so are *its main branches Septal lines at the bases* and also slight haziness in the right lower and mid-zones indicating interstitial pulmonary oedema

clouding may well be due to interstitial oedema of the connective tissue surrounding the hilum (Grainger, 1958).

2. *Pleural transudates.* They occur next in frequency are usually bilateral and basal but can be unilateral, the left side being more frequently affected than the right (Bedford and Lovibond, 1941).

3 *Chronic interstitial pulmonary oedema.* This is also a frequent finding, affecting mainly the bases of the lungs, *the appearances are very like those seen in mitral heart* disease (Fig. 42) The septal lines in left heart failure are less marked than in mitral heart disease and since pleural transudates are so common they are frequently obscured by the effusion. Similarly subpleural collections or extra-alveolar fluid and interlobar effusions

Grainger, 1958).

lobar fissures clear (Fig 43). On the lateral film the shadows occupy the central core of the lung leaving a clear peripheral zone.

The mechanism of the central distribution of the oedema is not yet clearly understood. One possible factor in mitral heart disease may be due to the basal arterial constriction deviating the blood to the middle and upper zones of the lungs. When, during an attack of acute cardiac asthma the blood flow in the middle and upper zones is increased and the pulmonary venous pressure rises, oedema will tend to appear in those areas of the lungs and not at the bases (Doyle *et al*, 1957).

The radiological shadows produced by acute pulmonary oedema can clear very rapidly, often within hours of their appearance.

Vascular distension within the lungs however may persist. The clearance rate of the oedema fluid depends largely on the type of exudate, the more albuminous the fluid the faster it will clear whereas fibrinous exudate may persist for a considerable time. Occasionally the changes may not resolve completely even within months or years. It has been demonstrated at post-mortem studies that these residual shadows are due to organizing intra-alveolar exudate (Doniach *et al*, 1954; Perry *et al*, 1957).

Uraemic Oedema of the Lungs

This unusual type of oedema occurring in left heart failure is usually associated with considerable renal impairment and its radiological and pathological features were reviewed by Doniach (1947). This author felt that oedema was due to a high pulmonary venous and capillary pressure and an alteration of capillary permeability due to uraemia. In uraemic [illegible] minimal, the only symptom being dyspnoea. This discrepancy is probably due to a rather solid rubbery consistency of the lung, "Solid oedema" and the associated fibrinous exudate. Unilateral distribution of "Solid oedema" is mentioned by Hodson (1950).

The mechanism for the central distribution of acute pulmonary oedema, and particularly of uraemic oedema, is still obscure It has been suggested by Herrnheiser and Hinson (1954) that there exists an anatomical and functional difference between the lung cortex, or central core of the lung, and the lung periphery, or medulla. In post-mortem angiographic studies, these authors demonstrated a difference in the anatomical relationship between the smaller pulmonary arteries and arterioles and bronchi in the peripheral lung field, from that seen in the larger arteries and bronchi in the central core of the lung. Some of the observations of Prichard *et al.* (1954) seem to agree with this anatomical difference. These authors were able to demonstrate distinctive flow patterns in acute animal experiments, injecting contrast material into the main pulmonary artery The bulk of contrast material appeared to be concentrated in the central core of the lung and only small amounts reached the periphery. In addition the lung periphery became ischaemic after the injection, with the ischaemia extending to the lobar borders along the interlobar fissures It appears therefore that some anatomical factors such as distribution and calibre of the smaller pulmonary arteries and arterioles as well as variations in the blood flow may play a part in the mechanism of the central distribution of pulmonary oedema.

to left-sided heart failure is an elevation of the pulmonary venous pressure above the level of the plasma colloid osmotic pressure. That other factors also operate is obvious since very high pulmonary venous pressures have been observed without the production of pulmonary oedema (Drinker, 1945; Hayward, 1955). (For further clinical and haemodynamic data readers are referred to Chapter 14.)

Acute Pulmonary Oedema

Since the patient is often too ill to be X-rayed in the department and only ward films are available, an adequate radiological examination is not always possible

In pulmonary oedema fluid accumulates in the alveolar spaces and produces a widespread radiological pattern of ill-defined shadows which may be quite extensive and confluent, simulating large areas of pulmonary consolidation with rather ill-defined borders.



FIG 43 4-ft chest film (Ward Unit) A P Patient with hypertension and acute left ventricular failure Consolidation of the central areas of both lungs, so-called "Bat's Wing" shadows due to pulmonary oedema

Alternatively, the shadows may be finer and more discrete with rather ill-defined borders to the opacities. Both lungs are usually affected symmetrically but the distribution may vary considerably with only one side affected, or there may be basal involvement or apical or central involvement.

Another type of radiological shadow due to the central distribution of the oedema fluid has been fully described by Doniach (1947) Hodson (1950) and Jackson (1951) This lesion was first observed by Day, *et al.* (1929), and Coe and Otell (1932) It is again referred to by Werkenthin (1939) and later discussed in more detail by Nessa and Riegler (1941), who coined the term "butterfly shadow". The condition was fully reviewed by Jackson (1951) who mentions the appearance of these "bat's wing shadows" due to central oedema in patients with mitral heart disease and cardiac asthma. The salient feature of the "bat's wing shadow" on a postero-anterior chest radiograph is the symmetrical distribution of a confluent non-homogeneous opacity extending from the hilum into the central lung fields leaving the periphery as well as the areas bordering the

arteries on the chest radiograph, the degree of intrinsic hilar pulsation, which is more marked in pulmonary hypertension than pulmonary stenosis, and some of the peripheral vascular appearances described before, will help to differentiate these conditions. Differential diagnosis from the Tetralogy of Fallot, or pulmonary stenosis associated with septal defects and right to left shunt, on radiological grounds, can be difficult. A right-sided aortic arch denies a closed septum. Angiocardiography is the method of choice to establish the diagnosis in most cases.

Pulmonary infundibular stenosis

Post-stenotic dilatation of the main pulmonary artery is absent and there is no visible pulsation on fluoroscopy. The appearances of the smaller peripheral pulmonary arteries

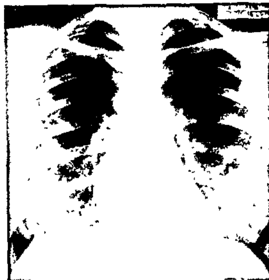


FIG 44 6-ft P A chest film Young female patient. Congenital pulmonary stenosis The main pulmonary artery is prominent due to post-stenotic dilatation, the peripheral branches are relatively small, marked pulmonary oligaemia

are very similar to those seen in valvular stenosis If valvular stenosis is also present the appearances are indistinguishable from pure infundibular stenosis. A bronchial pulmonary vascular pattern is rarely seen in either form of pulmonary stenosis.

The Heart in Pulmonary Stenosis

Right ventricular enlargement is an early sign of marked pulmonary stenosis and best seen on oblique and lateral chest films. Occasionally there may be right atrial enlargement and on fluoroscopy very vigorous pulsation can be noted over the right venticle

Following successful valvotomy some improvement in the degree of pulmonary oligaemia may be noticed; this is not easy to assess on either films or fluoroscopy. Reduction of the heart size may be considerable (Campbell and Brock, 1955).

Angiocardiography. This procedure can be of considerable help in defining the right ventricular outflow tract, the pulmonary valve and infundibular narrowing if present. The examination can be of value in the pre-operative assessment of the heart but is less valuable for the assessment of the pulmonary vascular appearances.

CONSTRICTIVE PERICARDITIS

A small main pulmonary artery with small peripheral branches and oligaemic lung fields are common findings in constrictive pericarditis. Although the pulmonary venous pressure is often elevated, radiological signs of this, such as septal lines are not present.

The heart shadow is either of normal size or even small Pericardial calcification is often seen, and on fluoroscopy there is diminished cardiac pulsation.

CONGENITAL HEART DISEASE

The radiological appearances of pulmonary vascular patterns in congenital abnormalities of the heart with increased pulmonary blood flow, due to a left to right shunt, and lesions with pulmonary hypertension and a right to left shunt have already been discussed in the section on pulmonary hypertension

In this section congenital abnormalities of the heart associated with obstruction to the pulmonary blood flow, and conditions where anatomical arrangements of the main pulmonary blood vessels are abnormal, will be described (for their clinical and haemodynamic assessment, see Chapter 9)

Pulmonary Stenosis with Intact Ventricular Septum

This can either be valvular or infundibular, or mixed. Pure valvular stenosis is the commonest variety, infundibular is less common and the mixed type is rare

Valvular pulmonary stenosis

Marked prominence of the main pulmonary artery is the most striking feature on chest radiographs with occasional slight dilatation of the right and left, or both, main branches. It has been shown by Holmann (1954) and Robicsek (1955) that post-stenotic dilatation of the pulmonary artery is largely due to turbulent blood flow distal to the stenosis damaging the elastic elements of the vascular wall. The degree of post-stenotic dilatation can vary considerably from case to case, for instance in mild pulmonary stenosis the radiological appearances can be normal. In the post-stenotic dilated section of the main pulmonary artery considerable intrinsic pulsation can be seen on fluoroscopy; this is absent in the main arteries at the hilum and beyond in the peripheral lung fields

In contrast to the appearances of the main pulmonary arteries the smaller peripheral branches are thin and narrow, producing a picture of generalized pulmonary oligaemia (Fig. 44); or, if the stenosis is slight, they may be normal. The peripheral vascular changes are very variable and depend largely on the degree of stenosis. Pulmonary oligaemia is difficult to estimate on standard chest X-ray, and even more so on fluoroscopy. By the use of contrast studies of the arterial tree vascular narrowing and under-filling is more convincingly demonstrated.

Differential diagnosis. Post-stenotic dilatation of the main pulmonary arteries with peripheral pulmonary oligaemia due to pulmonary stenosis must be differentiated from other conditions with a similar radiological appearance of the lung vascular pattern, as for example the Eisenmenger group. Absent, or only slight, dilatation of the main pulmonary

Angiocardiography. Angiocardiography is of particular value in outlining the outflow pathways of both ventricles, the overriding aorta, and in the demonstration of the type of pulmonary valvular stenosis, as well as the appearances of the pulmonary arteries distal to it (Fig. 45) Its main value lies in the establishment of a correct anatomical diagnosis and in the differentiation of the Tetralogy from other cyanotic congenital heart lesions. Selective angiocardiography with right ventricular injection is the method of choice in the Tetralogy. With this method a clear demonstration of the right ventricular outflow track and its relationship to the pulmonary artery and aorta will be demonstrated as well as the position and size of the ventricular septal defect and the type of pulmonary stenosis.

Appearances after operation. Successful valvotomy may improve the pulmonary blood flow sufficiently to produce a recognizable change in the pulmonary vascular filling.



FIG 45 Venous angiocardiogram Young girl, Tetralogy of Fallot Dextro-posed aorta fills

outlined

After a Blalock operation some increase in the pulmonary vascular filling may also be noted.

Unilateral rib notching is another radiological feature which may follow on Blalock's operation; it was first reported by Kent (1953) and again by Campbell (1958), and is due to the development of an extensive intercostal collateral circulation to the arm, following the division of the subclavian artery.

Transposition of the Great Vessels

In this congenital abnormality the pulmonary artery arises from the left ventricle and the aorta from the right. Intracardiac shunts at atrial or ventricular levels or a patent ductus are always associated, see Chapter 9. The position of the pulmonary artery and aorta relative to the left ventricle varies considerably and this may give rise to some difficulties at interpretation on routine chest films. When the aorta arises to the left it will form the left mediastinal border and will be very prominent. (Goodwin *et al.*, 1949). When the pulmonary artery arises centrally, it will not be clearly visible, and may be masked

Peripheral Pulmonary Artery Stenosis

Localized constriction of the major branches of the pulmonary arteries, probably due to congenital bands or strictures, is an unusual form of pulmonary stenosis, and has been described by Arvidsson *et al.* (1955) and Gyllenswärd *et al.* (1957). In some cases pulmonary hypertension proximal to the constriction sites have been reported (Falkenbach *et al*, 1959). Right ventricular enlargement may be considerable and the main pulmonary arteries are dilated proximal to the constriction. A definitive diagnosis can only be made by pulmonary arteriography

Fallot's Tetralogy

The radiological appearances of the heart and lungs in the Tetralogy are as variable as the clinical features. In the mild form of the anomaly, with only a slight override of the aorta and mild pulmonary stenosis, the radiological appearances of the heart and lungs can be quite normal On the other hand, in the severe form with gross overriding of the aorta and hypoplastic right ventricular outflow tract, marked right-sided cardiac enlargement, and marked peripheral pulmonary oligaemia will be seen on chest radiographs. Since in approximately 60 per cent of cases of the Tetralogy pulmonary stenosis is infundibular, post-stenotic dilatation of the main pulmonary arteries is not very common and a conclave left upper cardiac border is a usual finding. This, together with right ventricular dilatation, produces the characteristic "boot-shaped" appearance of the heart.

If valvular stenosis is present the main pulmonary artery and its left main branch can be considerably dilated, but not the right main branch. Considerable variations in size and shape of the main pulmonary arteries have been recorded on angiocardiographic studies by Pattinson and Emanuel (1957). These authors report that in one-third of the cases there was unequal division of the main branches, the left main pulmonary artery being larger than the right These authors have also concluded that inequality in size of the pulmonary arteries did not appear to affect the filling of the smaller peripheral pulmonary artery branches. The degree if peripheral pulmonary oligaemia is largely dependent upon the severity of the pulmonary stenosis.

Gross abnormalities of the pulmonary arteries distal to the pulmonary valve can occur, for instance, there may be absence of the left main pulmonary artery (Fig. 45), probably the most common variety. Other findings, such as extreme hypoplasia of both main branches of the pulmonary artery, or one main branch, have also been reported Emanuel and Pattinson (1956) reviewed the radiological appearances of an absent left main pulmonary artery and also considered the aetiology of this abnormality. When this condition is present post-stenotic dilatation of the right main pulmonary artery can occur and a marked discrepancy of the pulmonary vascular pattern of the two sides will be noted on chest films. A normal, or slightly attenuated vascular pattern will be visible in the right lung whereas in the left lung a bronchial pulmonary vascular pattern will be seen, the appearances of which will be discussed later.

If there is severe hypoplasia of the pulmonary arteries in addition to the attenuated pulmonary vascular shadows, a bronchial pulmonary vascular pattern may be visible, and this should be very carefully looked for.

aorta, above the hilum and to run into the lung field in an anatomical position different from normal pulmonary arteries (Goodwin *et al.* 1953). It may be difficult to differentiate, a large bronchial artery of this type from a pulmonary artery arising from a truncus arteriosus or from the aorta.

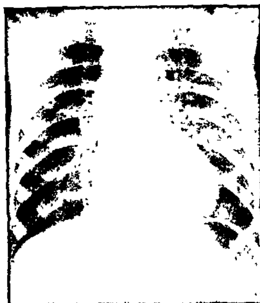


FIG 46 6-ft. P.A chest film Young boy. Fallot's

OTHER ABNORMALITIES OF THE PULMONARY ARTERIES

Congenital Absence of Pulmonary Artery

In these cases the normal vascular pattern will be replaced by a bronchial pulmonary vascular pattern, three such cases have been described by Wyman (1954) In one of these patients there was no associated cardiac anomaly; the other two had extensive congenital cardiac abnormalities. One case of congenital absence of the right main pulmonary artery was described by Madoff *et al.* (1952). These authors were able to demonstrate a bronchial supply to the lung by angiocardiography

Pulmonary Agenesis

This can be total affecting the whole lung, or it may be partial with absence of a lobe or lobar segment. On the chest film no pulmonary vessels will be visible in the affected areas.

Pulmonary Sequestration

In this anomaly of a lung segment there are usually associated cystic changes and no communication with normal bronchi. The sequestrated segment derives its blood supply not from the pulmonary artery but from an aberrant vessel arising from the thoracic aorta. The great surgical importance of this abnormal vascular supply has been stressed

by the aorta (Astley and Parsons, 1952). Irrespective of the position of the main pulmonary artery the hilar shadows appear full there is marked pulmonary plethora and intrinsic pulmonary pulsation will be noticed on fluoroscopy.

Transposition of the great vessels can be complicated by pulmonary stenosis (Cleland *et al.*, 1957) or the Eisenmenger reaction, see Chapter 9. In these cases the pulmonary vascular pattern will be very different from that described above since the lung fields will be oligaemic. The pulmonary arteries are difficult to identify—they may appear small and attentuated or they may not be visible at all, or only one side may be seen There is often considerable stippling around the hilar shadows, strongly suggestive of enlarged bronchial arteries. The heart shadow and mediastinum may present an unusual appearance with considerable right atrial and right ventricular enlargement and widening of the upper mediastinum, due to the anomalous position of the aorta and pulmonary artery

Special investigations. Angiocardiography is the most useful method in the investigation of transposition of the great vessels. In the uncomplicated group the relationship of the pulmonary artery and the aorta relative to the right and left ventricles will be clearly shown and so will be the appearance of the large vessels in the mediastinum In the lateral projection, the aorta will be seen to arise in front of the pulmonary artery, and in the antero-posterior projection the aorta may lie to the left, forming the left upper mediastinal border (Goodwin *et al.*, 1949) or the pulmonary artery may lie centrally (Astley and Parsons, 1952) more or less overlying the aortic root

In cases where transposition is complicated by pulmonary stenosis the main pulmonary artery may not be demonstrated, this does not exclude its presence, however, as has been shown by Cleland *et al*, (1957). In some of their patients the pulmonary artery was not visible on routine chest film or on angiocardiograms but it was present at operation In the differential diagnosis angiocardiography will help to distinguish transposition from other conditions of cyanotic congenital heart disease and in particular transposition with pulmonary stenosis from the Tetralogy of Fallot, tricuspid atresia and persistent truncus arteriosus (Cleland *et al.*, 1957).

BRONCHIAL PULMONARY ARTERY CIRCULATION

Normal bronchial arteries are too small to be visible on chest radiographs In a number of congenital cardiac and pulmonary artery anomalies the vascular supply to the lung is either predominantly, or entirely, dependent upon the bronchial circulation. In those cases the bronchial arteries can enlarge to a size so that they will produce a definite radiographic shadow

A bronchial blood supply to the lung can be seen in the severe Tetralogy of Fallot, pulmonary atresia, tricuspid atresia, persistent truncus arteriosus and marked hypoplasia of pulmonary arteries.

The radiological appearances of bronchial arteries in congenital heart disease were described by Taussig (1947) and Campbell and Gardener (1950). There is a rather coarse

be a fine lace-work pattern, probably produced by the [illegible]
(Fig. 46). Occasionally a very large dilated bronchial artery can be seen to arise from the

Aneurysms of the pulmonary artery are rare, they usually affect the main pulmonary artery, or one of the major branches. The dilated main pulmonary artery segment will be more localized than in generalized idiopathic dilatation; nevertheless the differentiation of the two conditions on the chest films may not always be possible and tomography or angiocardiography may have to be used, to establish the diagnosis.

ANOMALOUS PULMONARY VENOUS DRAINAGE

Anomalous pulmonary venous drainage can be partial or total.

Partial anomalous pulmonary venous drainage is fairly common and often associated with another congenital cardiac abnormality, particularly atrial septal defects.



FIG. 47 6-ft. P A. chest film of a boy. Atrial septal defect complicated by total anomalous pulmonary venous drainage "figure-of-eight" mediastinal shadow

Anomalous pulmonary veins from the right lung commonly drain into the superior vena cava or the right atrium, only one or both main veins may be affected. When one or both left pulmonary veins drain anomalously, they usually do so by way of a left superior vena cava or the coronary sinus Anomalous pulmonary venous drainage from the right lung, usually occurs without anomalous drainage from the left, whereas anomalous drainage from the left lung is often associated with a right-sided anomaly.

Total anomalous pulmonary venous drainage is uncommon. When it occurs, all pulmonary veins may drain into a common pulmonary vein and into a persistent left superior vena cava (Whital [illegible] for survival of the patient (for [illegible]

The radiological appear [illegible], site and origin of the anomalous veins and their effect on the re-circulation of blood through the right side of the heart and lungs. A single anomalous vein will rarely have an effect on

by Bruwer *et al* (1950), who pointed out that a number of patients had died at operation following haemorrhage from this abnormal vessel, thus stressing the need for an accurate diagnosis.

Special Methods of Investigation

Tomography can be most useful to demonstrate absence of a normal pulmonary artery pattern and also to outline large bronchial vessels. Angiocardiography is the method of choice to demonstrate absence of pulmonary arteries and to define bronchial vessels, particularly the smaller branches within the lung, and the larger branches as they arise from the aorta, or common trunk (Goodwin *et al.*, 1953; Davidson, 1956).

HYPOPLASIA OF THE MAIN PULMONARY ARTERY OR OF LOBAR PULMONARY ARTERIES

In the syndrome associated with abnormal transradiancy of one lung (Macleod, 1954) a number of factors can be responsible for the underlying pathology; (1) Vascular abnormalities, due to hypoplasia of the pulmonary artery; (2) Parenchymal pathology, such as emphysema; (3) Bronchial pathology, *i e* check valve mechanisms producing bronchial obstruction on expiration, as, for example, inhaled foreign bodies or bronchial adenoma.

The appearance of the lungs on chest radiographs is the same, irrespective of the cause The affected lung or the affected lobe will appear hypertranslucent and on fluoroscopy there may be mediastinal shift away from the affected side on expiration (Chapter 11). The lung vascular markings will be diminished and straightened and the arteries appear narrowed. On the chest film it is not possible to differentiate between true hypoplasia of the pulmonary artery and apparent narrowing due to diminishing blood flow. Although angiography will demonstrate arterial narrowing it does not help to differentiate between idiopathic hypoplasia and secondary hypoplasia due to diminished flow. Only correlation of lung function studies with anatomical findings on chest films or angiocardiograms will provide a satisfactory diagnosis (Belcher and Pattinson, 1957; Belcher *et al*, 1959).

IDIOPATHIC DILATATION OF THE PULMONARY ARTERY AND ANEURYSMS OF THE PULMONARY ARTERY

Idiopathic dilatation of the pulmonary artery is uncommon; it must be differentiated from secondary dilatation. The causes of secondary dilatation of the pulmonary artery have already been discussed in previous sections, *i.e.* the Eisenmenger syndrome, mitral stenosis, etc.

Minor degrees of pulmonary artery dilatation may be physiological as, for instance, in pregnancy, or occasionally in adolescence, or it may be associated with a high cardiac output such as thyrotoxicosis

As a rule the diagnosis is obvious when the radiological picture is correlated with the [illegible] there is any doubt, or if a very large pulmon- [illegible] iography may outline the pulmonary artery [illegible] but to make certain angiocardiography or [illegible] pulmonary arteriography should be used as the most useful diagnostic procedure (Goetz and Nellen, 1953).

defects in the contrast column due to streaming of blood at the site of insertion of the aberrant pulmonary vein in the superior vena cava and right atrium. Angiographic demonstration of individual pulmonary veins is not too satisfactory, except when the injection is made selectively by catheter into the vein from the right atrium or from the superior vena cava. When the pulmonary artery is selectively injected and the veins fill they may be seen to drain into the superior vena cava or into the right atrium.

By cardiac catheterization it is often possible to enter an anomalous pulmonary vein from the right atrium or superior vena cava and to establish the diagnosis (Fig. 48).

PULMONARY ARTERIO-VENOUS FISTULA

The first clinical diagnosis of pulmonary arterio-venous fistula was made by Smith and Horton (1939) It was soon realized that patients with arterio-venous fistula had also cutaneous and mucosal haemangiomas or teleangiectasis, confirming the hereditary nature of the disease. An extensive review of the literature and clinical data was presented by Sloan and Cooley (1953) and Le Roux (1959)

The clinical diagnosis of arterio-venous fistula can be confirmed by radiological methods of investigation.

Radiological Appearances

The most constant finding in arterio-venous fistula of the lung is the presence of an anomalous shadow in the peripheral lung field. Lesions are frequently multiple, they vary in size and shape from very small densities to large oval or round masses which may be multilocular. These shadows can occur in any segment or subsegment of the lung and may be concealed behind the heart shadow or lie close up to, or against the mediastinum, thus in addition to the postero-anterior film lateral and oblique projections are required. The peripheral shadow is often connected to the hilum by large vascular shadows representing afferent pulmonary arteries and efferent pulmonary veins These dilated vessels are better seen on the oblique and lateral films where they can be accurately localized to the fistula and the hilar shadow. The hilum may be markedly enlarged; calcification is rarely visible in the fistula The arterio-venous fistula can also receive part of its blood supply from the thoracic wall with the production of an unusual vascular shadow in the peripheral lung field close to the chest wall (Prutzmann and Flick, 1954).

Fluoroscopy. Intrinsic pulsation can sometimes be seen in the afferent vessels or the arterio-venous fistula itself. On respiration the shadow produced by the fistula can be seen to change its size This can be further enhanced by the Valsalva manœuvre which will decrease the size of the fistula, whereas the Müller manœuvre will increase it The normal change in size of the heart shadow with respiration and induction of the Valsalva manœuvre and the Müller manœuvre may be enhanced in the presence of a fistula.

Tomography. This is a most valuable method of examination since it can demonstrate the vascular supply to the fistula very clearly (Lindgren, 1946) (Fig 49) This is of great importance in the differential diagnosis since it may separate an arterio-venous fistula from other conditions producing similar peripheral shadows on the chest radiograph. Peripheral tumours or well circumscribed localized inflammatory lesions will not be

the heart shadow but since they are often associated with atrial septal defects or other congenital cardiac anomalies, the appearance of the heart can be abnormal and will depend upon the latter. If more than one vein drains into the right atrium, the augmented left to right shunt will further unbalance the lesser circulation, and affect the contour changes of the heart already produced by the intracardiac shunt. Thus right atrial and right ventricular enlargement can be marked associated with pulmonary hyperaemia. Even in the absence of an associated septal defect extensive anomalous drainage can mimic the radiological appearance of a septal defect.

Vascular changes An aberrant pulmonary vein may be visible on chest radiographs as it drains into the superior vena cava The veins may produce comma-shaped or thick



FIG 48 4-ft A P film of a boy with atrial septal defect Anomalous pulmonary venous drainage Cardiac catheter has entered the right upper lobe vein from the right atrium

vascular shadows close to the cardiac border and very often running parallel with it (Snellen and Albers, 1952; Bruwer, 1953; Sepulveda *et al.*, 1955). When the left and occasionally also the right pulmonary vein drains into a persistent left superior vena cava, this vessel together with the left innominate vein and a dilated right superior vena cava will produce an abnormal superior mediastinal shadow somewhat like a ring in appearance (Fig. 47). This ring shadow together with the heart shadow forms the "figure-of-eight" appearance of the mediastinum, originally described by Snellen and Albers (1952) and Gardner and Oram (1953) on fluoroscopy pulsation, can occasionally be noticed in this anomalous pulmonary venous ring (Hickie *et al.*, 1956).

Special methods of investigation. Tomography can be of value by demonstrating an aberrant vein more clearly and separating it from other mediastinal and hilar vascular structures (Stecken, 1959).

Angiocardiography was used by Sepulveda *et al.* (1955) in the investigation of their cases. Using venous angiocardiography these authors were able to demonstrate filling

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connected to the hilum by large feeding vessels; whereas the peripheral shadow may be very similar to that seen in a fistula.

Angiography is the most satisfactory method for diagnosis. (Sloan and Cooley, 1953; Weiss and Gasul, 1954; Steinberg and McClenahan, 1955). Since the fistulae are often multiple both lung fields must be completely covered by the examination and large films are therefore necessary (14 in. × 14 in.) when angiographic studies are carried out. Small arterio-venous fistulae may not be visible on the straight film but in the angiogram they are



FIG 49 A P tomogram left mid-zone Large lobulated peripheral pulmonary shadow connected by a vascular pedicle to the hilum, arterio-venous fistula and its vascular supply.

nearly always demonstrated (Steinberg and McClenahan, 1953). In addition to clear demonstration of the vascular supply, the fistula itself will be outlined as a dense shadow when filled with contrast medium.

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mild and limited in its extent. It may affect the pulmonary arteries down to the proximal parts of the segmental branches but rarely beyond this, and it takes a form that is significantly different from the ordinary atheroma of the systemic circulation. Pulmonary atheroma so-called consists of isolated round, or oval, cream-coloured plaques that are scarcely elevated above the surrounding intima. Histologically there is an accumulation in the intima of foamy phagocytes filled with cholesterol esters and enmeshed in a minimal quantity of fine collagen fibres. This lesion corresponds with the superficial fatty streaking seen in the aortas of young people but in the pulmonary circulation it does not progress to more severe grades in the absence of severe hypertension. In mild grades of hypertension this so-called atheroma becomes more extensive, though rarely confluent, and



FIG 50 Post-mortem angiogram from a normal control

spreads further down the segmental arteries. It retains its histological structure and being only flat thin plaque does not encroach on the lumen. The other change that is seen in the pulmonary arteries in mild hypertension is an increase in the muscular fibres of the media. This occurs in the elastic and muscular arteries and probably in the arterioles, but in practice, hypertrophy of this degree is extremely difficult to detect and its occurrence has been denied by O'Neal *et al.* (1955). The absolute thickness of the media naturally depends on the size of the artery in question, whilst the thickness relative to the diameter of the vessel depends on the degree of arterial tonus persisting after death and this in turn is variable. In practice it is possible to measure pulmonary arteries of elastic or muscular type if they have been artificially distended, preferably with some injection mass, after death, and such measurements can be compared with those found in arteries of the same calibre and from the same part of the lung in normal controls. Using this technique it is possible to demonstrate the presence of muscular hypertrophy in the media of both

CHAPTER 6

PATHOLOGY

By C. V. HARRISON

THE pulmonary vasculature is involved to some degree in nearly all diseases of the lung, but the vascular lesions that are clinically important are those associated with the pressure changes in the pulmonary circulation. It will, therefore, be convenient to consider the vascular pathology in relation to pressure changes rather than according to the morphology of the lesions. *In the other chapters the morbid physiology of the pulmonary* vasculature is discussed in relation to its clinical effects; in the present chapter therefore stress will be laid mainly on the structural changes that cause or are caused by alterations of function.

VASCULAR CHANGES IN PULMONARY HYPERTENSION

The vascular lesions that accompany pulmonary hypertension are not uniform but vary according to the pathogenesis and according to the severity of the hypertension. The following aetiological types of pulmonary hypertension are associated with different vascular changes.

Passive
Hyperkinetic
Organic vascular obstruction
Increased vascular tonus
Mixtures of the above

Passive Pulmonary Hypertension

In this group hypertension is the result of any change that impedes the venous outflow from the lungs, and therefore includes persistent left ventricular failure, mitral stenosis or incompetence, thrombosis in pulmonary veins or left atrium, congenital anomalies of venous drainage and left atrial myxoma. In its pure form passive pulmonary hypertension is only of mild degree but with severe impedance of pulmonary venous outflow a secondary arterial constriction is excited and can lead to very high pressures in the major pulmonary arteries.

In the less severe forms of passive pulmonary hypertension the changes in the vasculature are remarkably slight, so much so that they are difficult to detect by ordinary routine methods of examination and special techniques are necessary for the demonstration of

tween zones is accentuated, probably due to the relative increase in the muscular component, so that a difference between zones is perceptible in about three-quarters of the cases. At this level dilatation becomes uncommon in the upper zone and rare in the lower. Below the level where muscular arteries begin, that is at about 1 mm. diameter in the normal lung, there is usually a decreased visualization of arteries, particularly in the lower zones so that the background filling in angiographs is diminished. All these changes in fact correspond with those demonstrable angiographically during life but can be seen in greater detail. The histological counterpart of these lesions is mainly medial hypertrophy. In elastic arteries the medial muscle hypertrophies and at the same time the elastic fibres thicken. The final picture is an artery with coarse and irregular elastic fibres separated by unduly thick bands of muscle. This change extends down to the commencement of the muscular arteries. In the latter the response to hypertension is muscular



FIG 52. Radiograph of the middle lobe from the case in Fig 51 showing the uniform narrowing of the medium-sized arteries

hypertrophy. In both elastic and muscular arteries the degree of hypertrophy in severe mitral stenosis is of the order of two to five times normal and tends to be slightly greater in elastic arteries. In spite of individual variation from one artery to another the lower zone arteries are more hypertrophied than the upper zone by differences of about one and a half times (Fig. 53) Arterioles normally have a muscular media at their origin from the small muscular arteries, but soon lose this and consist of an elastic lamina and an intima. In mitral stenosis the muscular media spreads down the arteriole so that it comes to resemble a muscular artery only on a smaller scale Two other lesions are seen in the smallest elastic arteries, the muscular arteries and the arterioles: these are intimal fibrosis and medial necrosis. Concentric thickening of the intima by fibrous tissue is frequently seen and it often appears to reduce the lumen to nothing This appearance is an artefact due to muscular contraction being made permanent by histological fixation: there is much less narrowing in tissues fixed by arterial perfusion The relationship of this

elastic and muscular arteries in mild degrees of pulmonary hypertension such as that occurring in persistent left ventricular failure. *In arterioles muscle is only present in their* proximal parts and hypertrophy is not usually detectable unless hypertension has been relatively severe. On the venous side a similar hypertrophy occurs but is even more difficult to detect because, whereas arteries have clearly defined internal and external elastic laminae enclosing the muscle, veins have no clearly defined external lamina.

Mitral valve disease

With increasing obstruction to venous outflow pulmonary hypertension ceases to be purely passive in the sense of a transmitted back pressure, an increased tonus in the pulmonary arterial system is now excited. This is clearly demonstrable in cases of tight



FIG 51 Post-mortem angiogram from a case of

narrowed

mitral stenosis and severe cases of mitral incompetence. This medial muscular contraction persists after death and can be demonstrated in post-mortem angiographs and can be abolished by perfusion with sodium fluoride. As in angiograms taken during life, it is seen that the arterial tonus causes contraction of the arteries in a zonal manner; those arteries supplying the lower zones of the lungs have a significantly greater contraction than those to the upper zones. It should be noted that the distribution is related to the direction, upwards and downwards, and not to the anatomical lobes or segments. The post-mortem angiographic appearances in a typical case of mitral stenosis are as follows (Figs. 50, 51, 52). The main and the right and left pulmonary arteries are usually slightly dilated. The segmental arteries in the upper zone are usually of normal size but may sometimes be dilated; they are very rarely narrowed. The segmental arteries to the lower zones are either normal or contracted and may sometimes be dilated but there is a difference between upper and lower zones in about two-thirds of the cases. In the branches of the segmental arteries down to about the end of the elastic arteries, this trend towards a difference be-

tween zones is accentuated, probably due to the relative increase in the muscular component, so that a difference between zones is perceptible in about three-quarters of the cases At this level dilatation becomes uncommon in the upper zone and rare in the lower. Below the level where muscular arteries begin, that is at about 1 mm. diameter in the normal lung, there is usually a decreased visualization of arteries, particularly in the lower zones so that the background filling in angiographs is diminished. All these changes in fact correspond with those demonstrable angiographically during life but can be seen in greater detail. The histological counterpart of these lesions is mainly medial hypertrophy. In elastic arteries the medial muscle hypertrophies and at the same time the elastic fibres thicken. The final picture is an artery with coarse and irregular elastic fibres separated by unduly thick bands of muscle. This change extends down to the commencement of the muscular arteries. In the latter the response to hypertension is muscular



FIG 52 Radiograph of the middle lobe from the case in Fig 51 showing the uniform narrowing of the medium-sized arteries

hypertrophy In both elastic and muscular arteries the degree of hypertrophy in severe mitral stenosis is of the order of two to five times normal and tends to be slightly greater in elastic arteries In spite of individual variation from one artery to another the lower *zone arteries are more hypertrophied than the upper zone by differences of about one* and a half times (Fig 53) Arterioles normally have a muscular media at their origin from the small muscular arteries, but soon lose this and consist of an elastic lamina and an intima In mitral stenosis the muscular media spreads down the arteriole so that it comes to resemble a muscular artery only on a smaller scale Two other lesions are seen in the smallest elastic arteries, the muscular arteries and the arterioles these are intimal fibrosis and medial necrosis. Concentric thickening of the intima by fibrous tissue is frequently seen and it often appears to reduce the lumen to nothing This appearance is an artefact due to muscular contraction being made permanent by histological fixation: there is much less narrowing in tissues fixed by arterial perfusion The relationship of this

fibrous intimal thickening to passive hypertension is uncertain because a mild degree occurs as a normal age change and because its occurrence is irregular. Thomas *et al.* (1956) found that this type of intimal sclerosis was associated with thrombo-embolism and suggested that it results from this rather than hypertension with which it is less constantly associated. We certainly confirm the association of intimal fibrosis with other evidence of thrombo-embolism and agree with Thomas *et al.*, but it is worth noting also that in severe hypertension due to ventricular septal defect intimal fibrosis of this type is almost universal in small arteries and it is therefore possible that in some cases of severe pulmonary hypertension due to mitral stenosis intimal fibrosis may be a response to hypertension.

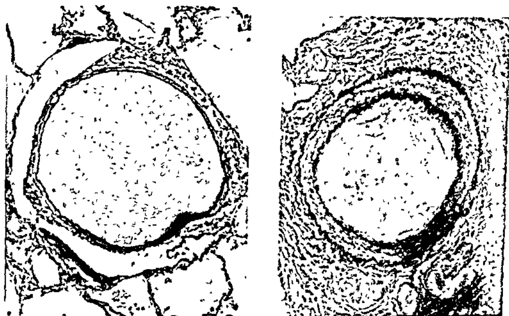


FIG 53 Differential muscular hypertrophy in mitral stenosis, same case as Fig 51. The artery on the left is from the apex of the upper lobe 15 mm from the pleura and shows only slight hypertrophy, the artery on the right is from the base of this lower lobe 15 mm from the pleura and shows gross hypertrophy (both × 110)

Necrosis of the wall of small pulmonary arteries with a consequent cellular response to the necrosis is a not infrequent finding in severe cases of passive pulmonary hypertension. These lesions were originally thought to be forms of rheumatic arteritis but Spain (1956) has shown that they do not correlate with rheumatic activity and they do correlate with severe hypertension, not only that due to mitral stenosis. The exact mechanism is uncertain but the evidence suggests that necrosis may follow intense spasm. Medial necrosis also occurs in infarcts and in their immediate vicinity, it is therefore essential to know the exact site of origin of the section before one can offer any opinion as to the nature of any arterial necrosis or intimal fibrosis. In fact we are of the opinion that random sections of the lung can be positively misleading

The veins also show hypertensive changes. There is again medial muscular hypertrophy and this too is greater in the lower zone (Fig. 54). There is also an increase in the

surrounding connective tissue but whether this is a response to venous hypertension or a response to chronic lymphatic distension and oedema is uncertain In veins of microscopic size, especially those within the secondary lobule, there is a curious type of intimal thickening. This takes the form of a layer of rather hyaline looking collagen with few nuclei and no elastic fibrils (Fig. 54). This change is common and occurs in all parts of the lung but does not affect all the veins.

The changes so far described are seen in cases of mitral stenosis, some of them only in cases with severe pulmonary hypertension. The question naturally arises, whether such changes occur in other forms of passive pulmonary hypertension. The answer is that the lesions in question are common to any type of passive pulmonary hypertension but that

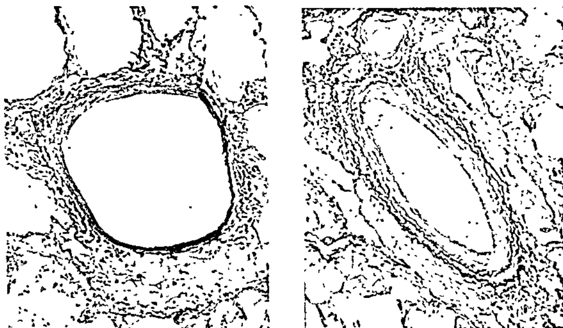


FIG 54 Venous hypertrophy in mitral stenosis, same case as Fig 51 These two sections of veins have been cut from the apex and base of the lung in the same positions as the arteries in Fig 53 The lower lobe vein (*right*) shows much greater hypertrophy It also shows a structureless, fibrous, intimal thickening (both × 70)

since some of them only occur with the more severe grades of hypertension they are rarely seen apart from mitral stenosis

The changes so far described can be regarded as direct consequences of passive pulmonary hypertension. There are other changes that are common complications and may be clinically important. Of these the two most important are atheroma and thrombosis and embolism. It was stated earlier that pulmonary atheroma is ordinarily of mild type and is comparable with superficial fatty streaking rather than with true atheroma. In cases of severe mitral stenosis this is no longer true and atheroma of the same severity and type as that seen in the coronary or other systemic arteries may be found This type of atheroma is thick enough to encroach seriously upon the lumen of medium-sized elastic

arteries and in angiograms it produces an irregular beaded outline (Figs. 55 and 56) Such obstructive atheroma occurs in about one-third of fatal cases of mitral stenosis and in our experience has been strictly limited to the lower zones. The actual lesion in the artery does not differ in any material way from the corresponding lesions in the systemic circulation and does not therefore need any detailed description. In practice there are infinite grades of severity between fatty streaking—so-called atheroma—and this severe type and in making this somewhat arbitrary distinction into two types we have taken as our criterion the presence or absence of any perceptible degree of narrowing in the angiogram. In many cases histological sections show evidence of the incorporation of thrombus into the atheromatous lesions. This raises the whole problem of the part played by



FIG 55 Post-mortem angiogram from a case of severe mitral stenosis The lower zone arteries are narrowed, but in addition they show points of extra narrowing due to atheroma, particularly in the posterior basal segment

thrombosis in the genesis of atheroma which is not a proper subject for present consideration. It is however fair to say that in the pulmonary circulation there is ample evidence for the incorporation of thrombus into obstructive lesions (Fig 57) and there is a statistical association in our experience between the presence of obstructive atheroma and the presence of manifest thrombo-embolic lesions Furthermore, we have noted that atheroma is significantly more severe in the sense of causing obstruction in cases of mitral stenosis than in cases of hyperkinetic pulmonary hypertension. This observation implies that some factor other than hypertension is involved and since mitral stenosis is commonly associated with a diminished flow this factor might be thrombosis. The other factor that is of importance in mitral stenosis is thrombo-embolism. In our experience there are total arterial occlusions demonstrated by angiography in a half of all cases and there are infarcts in three-quarters of these. This incidence of vascular occlusions in a half of the cases is

so very high that it is improbable that they are all ordinary emboli even if all possible allowance is made for the liability of bed-ridden patients to venous thrombosis. One is therefore forced to the conclusion that a significant proportion of the arterial occlusions are the result of local thrombosis. The distribution of arterial occlusions in mitral stenosis is the same as the distribution of emboli. In a personal series of 132 arterial occlusions from 29 lungs 100 were in the basal arteries of the lower lobe and in the middle lobe (or lingula) The remaining 32 being in the upper lobe and apex of lower lobe. In the same lungs there were 50 infarcts, or infarct scars, 42 being in the basal segments and middle lobe and eight in the upper lobe and apex of lower lobe. *This distribution is essentially* similar to that of occlusive atheroma and may indicate the liability for thrombosis to

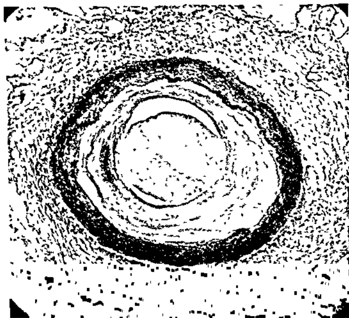


FIG [illegible]

occur over atheromatous lesions. A similar distribution is however seen in undoubted emboli and Short (1951) in an unselected series of cases of pulmonary embolism found the lesions in the lower zones in five-sixths of cases In some of the cases mentioned above *it was possible by dissection to demonstrate both embolus and propagated thrombus* whilst in others there was evidence for the thrombus having occurred locally. There seems to be little doubt that both embolism and local thrombosis occur, what remains uncertain is their relative proportions. Whatever may be the origin of pulmonary infarcts in mitral stenosis, they have an ill effect for the patient, especially if they induce pleural effusion. In every case with persistent pleural effusion it was possible to demonstrate old infarction in the underlying lung implying that the infarction, usually major or multiple, was the cause of the effusion. Since a pleural effusion involves pulmonary collapse it necessarily

involves a decreased blood flow through the part of the lung that is collapsed. In the presence of right ventricular strain this additional obstruction to pulmonary blood flow may well be a serious matter.

Effects of mitral stenosis on the lung parenchyma

Three effects need mention, passive congestion, Kerley's lines and ossification.

Passive venous congestion doubtless occurs in the lungs in cases of passive pulmonary hypertension yet the appearances of the lungs at autopsy may not reflect this as clearly as one expects. The reason is that the lungs at autopsy tend to reflect the mode of dying



FIG [illegible]

14, 766)

rather than the events preceding death. The classical picture of intensely engorged alveolar walls with bulging capillaries described by Parker and Weiss (1936) is practically only seen in patients who die in acute pulmonary oedema. In these cases there is usually a curious distribution of the congestion and oedema whereby they occur mainly in the central and upper parts of the lung leaving the basal segments and especially the distal half of the middle lobe free or only mildly affected (Figs. 58 and 59) This distribution corresponds to that of the hilar or central pulmonary oedema seen in X-rays during life.

In patients who die in congestive cardiac failure the lungs may be engorged with blood but more often engorgement is slight, especially if cardiac failure has been vigorously treated. A more constant finding is siderosis. This can be found in some degree in every

case of mitral stenosis with pulmonary hypertension. In general, haemosiderosis increases with the severity of the mitral stenosis and is seen most strikingly in cases with severe pulmonary hypertension. Anatomically, the deposits of haemosiderin are scattered throughout the lung in a series of foci usually 2–3 mm. in diameter. The distribution is even through different parts In severe cases these foci may be numerous and large enough to cast shadows on an X-ray film and produce a fine snow-storm appearance. Microscopically the foci consist of groups of adjacent air spaces filled with pulmonary phagocytes



FIG. 58 Zonal congestion Left lung of a patient with mitral stenosis and severe pulmonary hypertension, who died in acute pulmonary oedema The congestion is confined to the central and upper zones

packed with haemosiderin granules, so-called heart-failure cells In rare cases iron pigment may encrust on the surface of pulmonary elastic fibres, apparently rendering them rigid and brittle The peculiar focal distribution of pulmonary siderosis has given rise to speculation as to its pathogenesis. All workers are agreed that the haemosiderin comes from the breakdown of spilt blood. Some have suggested that this peculiar distribution is due to haemorrhage occurring at or near the foci themselves and have postulated bleeding from bronchopulmonary vascular anastomosis (Lendrum *et al.*, 1950). Against this it has been pointed out that just such focal accumulations of phagocytes will occur as part of the normal clearing mechanism of the lungs—that pulmonary phagocytes always

collect into such foci when they have picked up particulate matter from alveoli. From experimental evidence in animals and from the observation of dust phagocytosis in man it appears that there is no need to postulate bleeding near the sites of subsequent siderosis because such focal accumulations will follow quite diffuse bleeding.

The undoubted fact that focal collections of phagocytes will always follow diffuse phagocytosis does not of course disprove the existence of communications between the pulmonary and bronchial circulations. In mitral stenosis it has been suggested that pulmonary–systemic communications on the venous side could relieve the pulmonary venous pressure by diverting blood to the systemic veins. The ordinary bronchial veins drain into pulmonary veins, but Gilroy *et al.* (1952) have shown that the pleuro-hilar

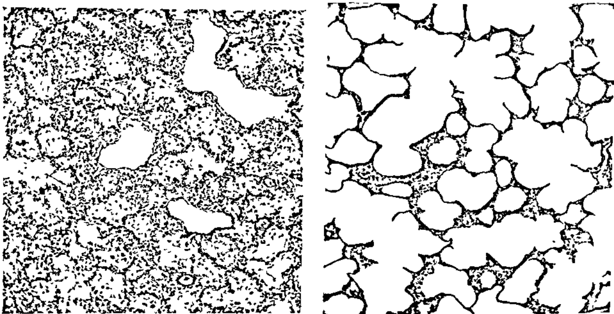


FIG 59 Zonal congestion Upper (*left*) and lower (*right*) zones of the lung of a man of 22 with mitral stenosis who died in acute pulmonary oedema Congestion is seen only in the upper zone (both ×42).

bronchial veins do drain into systemic veins and could decompress the pulmonary veins in cases of pulmonary venous congestion. They further claim that these pleuro-hilar veins are unduly engorged in cases of mitral stenosis seen at thoracotomy, implying that such decompression does occur.

Septal lines. The exact basis of the thin straight lines of opacity described by Kerley has been the subject of speculation and controversy but there now appears to be adequate evidence that they are caused by the opacity of interlobular fissures that happen to lie in alignment with the plane of the X-rays in a chest film. Normally such fissures are too thin to throw a shadow but in conditions of severe venous back pressure they become widened sufficiently to be visible in contrast with the aerated lung on either side This widening is due to two changes. The one is distension of the lymphatic vessels within them, the other, and probably the greater, is oedema of the loose connective tissue of the septa themselves (Fig. 60). Obviously there are septa between all the lobules and many of them will be

widened but only a limited number, and in practice those near the periphery, will happen to lie in a plane where they can cast a shadow.

FIG [illegible]

Pulmonary ossification. In a minority of cases of severe mitral stenosis foci of bone are found in the lung. Usually these are scanty but in occasional cases they are numerous and give characteristic X-ray shadows. Usually they are about 3–5 mm. diameter. Histologically they consist of well-formed, usually lamellar bone, and occupy a group of adjacent

air spaces which they fill so exactly that they must have been formed *in situ*. Unfortunately no one has reported observing the early stages of such a formation. Pulmonary ossification of this type is relatively rare. It occurs chiefly in males, can occur in any part of the lung and occurs only when both pulmonary venous and arterial pressures are raised, *i e.* in passive pulmonary hypertension (Heath and Edwards, 1959). Fleming and Robinson (1957) have suggested that the ossification follows subclinical pulmonary oedema but so far there is a singular lack of factual evidence regarding the origin of these lesions. We believe that pulmonary ossification is relatively much commoner than is generally believed. In a personal series of 40 cases of mitral stenosis bone was found by X-rays and confirmed microscopically in eight (20 per cent) but in only one of these were the lesions numerous enough to have been recognizable during life.

It should perhaps be made clear that pulmonary ossification in mitral stenosis is quite distinct from the rare condition of microlithiasis alveolaris pulmonum.

HYPERKINETIC PULMONARY HYPERTENSION

Under this heading are grouped the cases in which blood reaches the pulmonary arteries in either an excessive volume or with an excessive force The first occurs typically in atrial septal defect with left to right shunt. The second occurs when there are communications at ventricular or at aorto-pulmonary level. In atrial septal defect there is usually an excessive flow but the pulmonary vascular resistance is low—at least for a time—and consequently there need not be any very significant pulmonary hypertension. On the other hand if there is communication of major degree at ventricular or at aorto-pulmonary level the systolic force of the left ventricle will be transmitted to the pulmonary artery, always provided that the communication is large enough and that in ventricular septal defect the lungs are not protected by a coincident pulmonary stenosis. If the pulmonary artery is exposed to the left ventricular force a high vascular resistance is inevitable if the cardiac output is to be reasonably divided between the pulmonary and systemic circulations: a low pulmonary resistance would permit too great a proportion to pass to the pulmonary circulation with consequent starving of the systemic circulation. Edwards (1957), who has particularly stressed the importance of the pulmonary vascular resistance, refers to high resistance and low resistance types of hyperkinetic hypertension. Pulmonary vascular resistance depends partly on the total vascular capacity of the lungs but in practice this is so great that the right ventricular output has to reach very high values (over 16 litres/min.) before the capacity of the vasculature of itself offers serious resistance.

The more important mechanism in pulmonary vascular resistance is the tonic contraction of the pulmonary arterial system, particularly the muscular arteries. In uncomplicated cases of hyperkinetic pulmonary hypertension the vascular resistance, whether high or low, is provided by muscular tonus and the arteries undergo muscular hypertrophy in response to their increased load. This state of affairs Edwards has described as one of high resistance with high reserve, implying that the hypertrophied pulmonary arteries are capable of relaxation Such a state only persists for a limited time, a time that appears to depend on the height of the pulmonary arterial pressure. After this secondary changes occur in the pulmonary vasculature in the form of intimal thickening and actual luminal occlusion

to such an extent that relaxation of vascular resistance is diminished or even impossible. This is the high resistance—low reserve state. The effects of hyperkinetic pulmonary hypertension on the pulmonary vasculature are very much the same whatever the underlying lesion but they are affected to some degree by the flow, the age of onset and the height of the pulmonary blood pressure. For this reason it will be convenient to consider separately the lesions in atrial septal defect, ventricular septal defect and aorto-pulmonary communications.

Atrial Septal Defects

Many patients with atrial septal defects do not have pulmonary hypertension; in any case hypertension does not occur for many years and usually not until the third or fourth decades and some patients never develop it. In patients who die without developing



FIG 61 Atrial septal defect Post-mortem angiogram from a woman of 45 The larger arteries are greatly dilated, the small peripheral branches are narrowed and scarcely visible

pulmonary hypertension the main pulmonary arteries and the larger elastic arteries usually show simple dilatation. Arteries of microscopic dimensions, however, do not show any recognizable hypertrophy or other lesion (Heath and Whitaker, 1957). With the onset of hypertension the first response is hypertrophy of the muscular media in the arterioles and small muscular arteries. This is a reversible change and the pulmonary vascular resistance is still labile and is reversible on closing the septal defect With more severe grades of pulmonary hypertension or if it persists for longer periods the pulmonary vascular resistance becomes fixed and structural changes occur in the vasculature so that with operative closure of the defect a return to normal is no longer possible. It will be easiest to describe the findings in a typical case of atrial septal defect coming to autopsy

In the typical case the main pulmonary artery and its right and left branches are enormously dilated, the diameters being about twice normal or even greater. The same is true of the segmental arteries and their first or second divisions but distal to this there is a

rapid reduction in the excessive size so that at the end of the elastic arteries the lumina are approximately normal (Fig. 61). This is at the level where the arteries have a lumen of about 1 mm. and in straight arteries lies about 10–15 mm. from the pleura. This dilatation



Fig 62 Sections of the posterior basal branches of the pulmonary arteries from cases of ventricular septal defect (*upper*) and atrial septal defect (*lower*). The former shows regular parallel elastic laminae, the latter shows irregular elastic laminae (elastic stain, both × 95)

is similar in all zones. In the muscular arteries there is a reduction in lumina so that in angiograms of injected lungs the background is poorly filled. On dissection the dilated elastic arteries show premature atheroma, but the latter is not usually severe and virtually never encroaches visibly on the lumen. Within these dilated, atheromatous arteries, local

thrombosis may occur, usually between the entry of the pulmonary artery into the lung and its break up into lobar and segmental branches. The thickness of the main pulmonary artery and its branches varies. Ordinarily it is hypertrophied but with what amounts to aneurysmal dilatation the right and left pulmonary arteries are usually thinned down to about normal thickness and even less. Distally, in segmental pulmonary arteries there is hypertrophy of both muscular and elastic elements so that the artery wall is twice or thrice normal thickness in spite of dilatation. It has recently been observed (Heath *et al.*, 1959) that the elastic fibre pattern of the pulmonary artery differs in congenital and acquired pulmonary hypertension. In foetal life the aorta and pulmonary artery are similar, having evenly spaced, parallel, layers of elastic tissue. In the aorta this pattern continues throughout life, but in the pulmonary artery after birth involution occurs, the elastic tissue becomes



Fig [illegible]

irregular, and the laminae have breaks in their continuity. If, owing to congenital heart disease, the pulmonary artery pressure fails to fall after birth, the pulmonary artery fails to involute and retains its foetal, aorta-like elastic pattern. If, however, hypertrophy occurs after involution has taken place the hypertrophied artery develops thickened but irregular bands of elastic tissue. Thus, in atrial septal defect, and in all forms of acquired pulmonary hypertension, the pulmonary arteries have irregular elastic tissue, whilst in ventricular septal defect and other conditions with pulmonary hypertension from birth the pulmonary arteries resemble the aorta in structure (Fig. 62). We have confirmed these observations and noted that they extend down the length of the elastic arteries. In the muscular arteries there is true muscular hypertrophy and this extends down to involve the proximal parts of the arterioles. In these muscular vessels it is common to find various obstructive intimal

lesions. The latter are focal and irregular but are more numerous in cases with greater hypertension and in fact Heath has found a direct correlation between the grades of arterial damage and the height of the pulmonary blood pressure. Three basic lesions are seen. The simplest is a concentric intimal proliferation of fibrous tissue with few or many elastic fibres leading to virtual obliteration of the lumen even when it has been distended by perfusion after death. The second is the presence of a cellular proliferative mass containing multiple very small channels lying within a small artery or in an arteriole just distal to its origin from a parent branch and usually with partial or complete destruction of the originally surrounding medial wall—a lesion that resembles a renal glomerulus (Fig 63) The third lesion is a "blown out" arteriole with a grossly dilated lumen and a thin wall running a tortuous course from an origin from one of the cellular lesions and ending in pulmonary capillaries. The combination of concentric intimal fibrosis and these curious complexes obstructs the blood flow and produces a very high and irreversible pulmonary vascular resistance; high resistance—low reserve type of lesion of Edwards There has been much speculation as to the nature and origin of these complex lesions and whilst their mode of origin is still uncertain it is certain from serial section reconstructions that they are not bronchopulmonary or arteriovenous anastomoses as was originally suggested, but lie wholly within the pulmonary arterial system (Wagenvoort, 1959). The relationship between the glomerulus-like body and the dilated arterioles is not constant The sequence described above is in our experience the commonest but either can occur alone and sometimes the dilated arteriole arises proximal to the glomerulus-like body and has been described as an "anastomosis". Two other lesions may be seen, thrombosis of small muscular arteries and necrosis of the walls of small arteries. The former is fairly common in severe cases, the latter is rare

Venous changes are slight, some intimal fibrosis may be seen in small radicles in most severe cases, presumably in response to the high flow because there is no passive hypertension.

The lung parenchyma does not show any constant change as it does in passive hypertension. Siderosis is normally absent but has been recorded Other changes such as fibrosis are the results of coincidental infarction.

Ventricular Septal Defects

The essential lesion in ventricular septal defect is a direct communication between the left ventricle and the pulmonary artery whereby the latter is subjected to the full force of the left ventricular pressure. Clearly the extent to which it is so exposed depends on the size of the communication and Edwards (1957) has shown that it is the size and not the position of the defect that matters. If the defect is small in relation to the aortic orifice there will be a shunt of blood from the left ventricle to the pulmonary artery but there will not be any significant pulmonary hypertension. If the defect is large, that is near the size of the aortic orifice, then there will be full communication between the two circulations. Clearly if there is to be a reasonable division of the circulations and an adequate flow through the systemic circulation the pulmonary vascular resistance must be similar to the systemic vascular resistance. Such a state of affairs is normally present at birth when the pulmonary arteries are as thick as the corresponding systemic ones. Normally

the pulmonary arterial tree involutes during the first few months of extra-uterine life but with a major ventricular septal defect no such involution can occur and the pulmonary arteries remain as thick and muscular as systemic arteries. It may be added in parenthesis that in some children the pulmonary vasculature appears to fail to retain its original musculature and resistance and the children die of heart failure from excessive left to right shunting early in life. In the majority of cases the hypertrophied pulmonary vasculature exerts a sufficient resistance to produce a reasonably balanced circulation At first the effect on the pulmonary vasculature is purely one of hypertrophy, or perhaps more correctly lack of normal atrophy. At this stage the main pulmonary arteries and their major divisions show muscular and elastic hypertrophy, being as thick as the corresponding systemic arteries, furthermore the elastic tissue in them lies in regular parallel lamellae

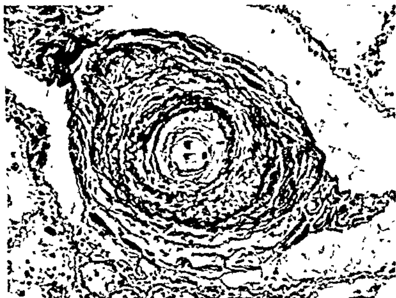


FIG 64 Small muscular artery in ventricular septal defect The media is greatly hypertrophied The internal elastic lamina is wrinkled and the lumen is reduced by fibro-elastic thickening of the intima (elastic stain × 200)

separated by regular layers of muscle and giving a pattern exactly like that of the aorta. The muscular arteries show muscular hypertrophy to a thickness comparable with normal systemic arteries. The arterioles show a spread of muscle distally so that they have muscular walls down to a size much smaller than normal The veins and lung parenchyma are normal. At this stage the reaction is physiological and reversible. The pulmonary vascular resistance can be lowered by drugs and after successful cardiac repair the pulmonary artery pressure and pulmonary vascular resistance falls (Heath *et al.*, 1958b). How long this reversible state lasts depends on various factors, but it is probably only for a few years that the pulmonary circulation can withstand systemic blood pressures. After this the smaller muscular arteries develop fibroblastic intimal thickening with reduction of the lumen This appears to fix permanently the contracted state of the artery because we have noted that even after artificial distention the elastic lamina surrounding this intimal

thickening is wrinkled (Fig. 64). This intimal fibrosis is patchy along the length of the arteries so that a histological section showing limited numbers of affected arteries gives a false impression of the true degree of vascular obstruction. Medial necrosis is not infrequent and is again local and patchy and the healing of such necrotic foci is the probable origin of patches of arterial wall where collagen has replaced muscle and elastic tissue (Fig. 65). Beside these there are glomerulus-like bodies and blown-out dilated arterioles often forming angiomatous masses. In the larger elastic arteries there is uniform dilatation but in our experience it is of limited degree and significantly less than that seen in atrial



FIG 65 Ventricular septal defect Muscular artery showing destruction of the media around most of the circumference, dilatation and intimal fibrosis A small branch shows intimal fibrosis (elastic stain × 100)

septal defects. With the narrowing of the majority of the muscular arteries, angiograms give a characteristic picture of slightly dilated elastic arteries suddenly narrowing down and leaving an underfilled periphery (Fig. 66) Besides this dilatation there is premature development of atheroma and a tendency to thrombosis. By this time the pulmonary vascular resistance is very high and fixed. Between the pure muscular hypertrophy of the early stages and this gross degree of organic narrowing there are obviously intermediate degrees of damage. Heath and Edwards (1958) have described six grades from simple [illegible] to extreme damage. They have been able to correlate these morphological [illegible] e operation and its [illegible]

Patent Ductus Arteriosus

The effects of persistent patency in the ductus depend upon the freedom of communication between the two arteries. If the ductus is long or narrow there is a left to right shunt but no significant transmission of pressure. If it is short and wide there will be increasing

transmission of pressure. In so far as left ventricular pressure is transmitted to the pulmonary artery the effects of a patent ductus are essentially like those of a ventricular septal defect and produce similar lesions in the vasculature. There appears to be a tendency to localization of atheromatous lesions in the pulmonary artery close to the ductus and dissecting aneurysm of the pulmonary artery has been recorded (Whitaker *et al*, 1955), but in other respects there is no essential difference between the effects of a patent ductus and those of a ventricular septal defect, except that in general those of a ductus develop later.

Other Congenital Cardiovascular Malformations

It would be impossible to list all the possible malformations and their effects on the pulmonary circulation nor is it necessary to try. As a generalization it may be said that

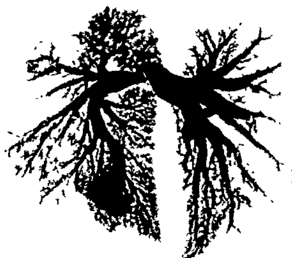


FIG 66 [illegible]

lungs were injected simultaneously)

three effects can occur; left to right shunting, transmission of pressure from left to right and oligaemia of the pulmonary circulation The effects of the first two have been described and the effects of pulmonary oligaemia will be considered in a later section.

PULMONARY HYPERTENSION DUE TO ORGANIC VASCULAR OBSTRUCTION

Obstruction of the pulmonary vascular territory may occur from occlusions within the lumina of the vessels, from lesions of their walls or from loss of lung substance. The pulmonary vascular tree may be obstructed by emboli of all types or by thrombosis *in situ*.

Pulmonary Embolism

Pulmonary embolism due to impacted thrombus may conveniently be divided into four types, massive, multiple, incidental and multiple minute. Massive pulmonary embolism implies the sudden occlusion of the major part of the pulmonary circulation by the impaction of a mass of embolus. Usually the latter comes from the major lower limb veins and impacts at the bifurcation of the pulmonary artery in the form of a coiled-up mass Sometimes the mass breaks up and passes into the right and left pulmonary arteries. In any case the majority of the pulmonary circulation is cut off and death follows rapidly. There is no infarction and the lungs show no characteristic change. The right heart at autopsy is dilated and tends to bulge in the conus, this is however not reliable and may be absent if autopsy is not performed soon after death.

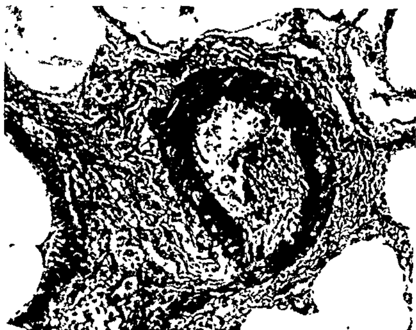


FIG 67 Multiple minute pulmonary emboli Woman of 27 who died of an apparent idiopathic pulmonary hypertension The microscopic pulmonary arteries contained innumerable obstructions apparently due to organizing emboli Section of a small artery showing such an obstruction, unorganized thrombus is still visible (× 150)

Multiple pulmonary embolism is a state where, over a period of hours or days, emboli of smaller size impact in segmental pulmonary arteries or their branches; often at the divisions of the segmental arteries. Sufficient emboli impact to obstruct the majority of the circulation and death results from acute right ventricular failure. The importance of recognizing this group is that, unless the segmental pulmonary arteries and their first divisions are deliberately dissected, the presence of a fatal number of emboli will not be recognized. Incidental pulmonary emboli are those found on routine dissection of the pulmonary arteries in small numbers and not apparently contributing to death in any

major way. It is not always possible to tell whether these are emboli or locally formed thrombi and there is reason to believe that some at least are the latter.

Finally, there is a small group of cases which present as apparent examples of primary pulmonary hypertension At autopsy no emboli or thrombi can be recognized by macroscopic dissection but on histological section many small arteries, often about 1 mm. diameter, are wholly or partially occluded by fibrous intimal thickenings that are irregular in distribution and often divide the lumen into two or more channels. Organizing fibrin can often be found and there is little doubt that the obstructions are produced by the organization of thrombus (Fig. 67). What is not certain is whether the thrombus was transported as embolus or whether it was locally formed as a result of damage to the vessel wall and perhaps other factors. The assumption of embolism is based on the exact resemblance between the lesions in these cases and lesions found in cases of undoubted repeated embolism. The belief is also supported by the ease with which such lesions can be reproduced by showers of small emboli in animals. It is, however, fair to point out that such evidence does not amount to proof and the true pathogenesis of these cases remains uncertain. They are of academic rather than practical importance because of their rarity; we have had three such cases among some eight thousand autopsies and a limited number of similar cases have been reported in the literature (Belt, 1939; Castleman and Bland, 1946).

Incidence. The incidence of pulmonary embolism is difficult to assess. The following figures are derived from the records of the Department of Pathology at the Postgraduate Medical School for the decade from January, 1948, to January, 1958. It is probable that they are a fair sample since rather similar figures have been published from other sources (Parker and Smith, 1958)

Total autopsies	4,075
Cases of pulmonary embolism	169
Incidence	4·2%

Types of emboli

Massive	47% of emboli	2% of autopsies
Multiple	36% „ „	1 5% of autopsies
Incidental	17% „ „	

169 cases of pulmonary embolism

Cancer (without operation)	51	(30%)
Surgery within one month	43	(26%)
Other non-cardiac diseases	44	(26%)
Heart disease	31	(18%)

These figures suggest that surgical operations account for only about a quarter of cases and that immobilization in bed and the debility caused by the underlying disease accounts for the other three-quarters If these figures are broken down according to the type of embolus found the following figures are obtained.

169 cases of pulmonary embolism

	Massive	Multiple	Incidental
Cancer without operation . .	24	15	12
Surgery within one month . .	28	12	4
Other non-cardiac disease .	17	18	7
Heart disease	9	16	6

These figures suggest that malignant disease is accompanied by a high incidence of all types of embolism, surgery (including a single obstetric case) is followed mainly by major embolism, whilst cardiac disease accounts for a disproportionately high proportion of small emboli. The latter figures are liable to two inaccuracies. In a limited series of cardiac cases investigated in detail by angiography the incidence of incidental and multiple emboli was much higher than the above total figures, suggesting that in routine autopsies small incidental emboli are often overlooked. It further suggests that a proportion of the cases of so-called minor embolism are in fact cases of local thrombosis occurring in diseased arteries with a disordered circulation. The probable truth of the latter finding is suggested by the fact that a high proportion of "emboli" in mitral stenosis occur in arteries of one particular size

Site of embolism. Short (1951) found that five-sixths of emboli involved the lower zones and Parker and Smith (1958) also found a high incidence in the lower lobes and also that the right lung was more often affected than the left. Similar results have been obtained with experimental embolism in animals and there is good evidence to suggest that the site of impaction of emboli is governed largely by the direction of flow of the axial stream in the main pulmonary arteries.

Effects of embolism. In the absence of heart failure emboli rarely cause infarction. Even in the presence of heart failure, emboli are far more numerous than infarcts. From our own findings infarcts are commoner in cases of mitral stenosis than in cases of heart failure from any other cause The reason for this is that normally infarction is prevented by a collateral blood flow from bronchial arteries to pulmonary capillaries. A rise of pulmonary venous pressure tends to resist such a flow and so prevents the establishment of an adequate collateral circulation (Liebow *et al.*, 1959) Since the highest pulmonary venous pressures occur in mitral stenosis, infarction will be most likely to occur in this disease. It is worth noting that pulmonary infarcts are not quite like other infarcts. In other tissues an infarct always involves necrosis of the tissue, in the lung there is always haemorrhage into the alveoli due to ischaemic damage to the alveolar capillaries, but there is not always total necrosis of the alveolar wall. As a consequence, the results of infarction are not uniform. If there has been full necrosis of tissue there is a focus of fibrous scarring [illegible]

area.

Non-thrombotic types of pulmonary embolism

Air embolism. This is mainly of interest in forensic pathology, though the possibility of its occurrence cannot ever be neglected. Simpson (1942) encountered 56 cases in ten years' forensic work and ten of these occurred during operations and four during pneumo-

thorax or thoracotomy. He points out that whilst it may take a few hundred millilitres of air to kill a healthy adult much smaller quantities may prove fatal in a severely ill patient and he estimates that as little as 15 ml. may suffice in some cases.

Fat embolism. This is a common occurrence but a rare fatality. Rare that is, in patients who are not seriously injured. Robb-Smith (1941) found that among traumatic deaths coming to autopsy there were 70 with fractures outside the skull and of these 30 had gross fat embolism and in 21 it was probably a significant factor causing death. With the improved treatment of traumatic shock it is likely that fat embolism may assume greater importance In the majority of cases death is not directly due to acute right heart failure, from which the patient usually recovers, but from embolism of the small cerebral arteries with death in coma.

Bone marrow embolism. This is a recent finding of purely forensic importance. In major fractures particles of bone marrow are driven into the circulation and embolize small pulmonary arteries. Mason (1958) has found such embolism in 40 per cent of air-craft fatalities. The incidence is significantly lower than that of fat embolism but the embolism occurs with extreme rapidity and is of value in determining whether injuries occurred before or after death. Marrow embolism is of no clinical significance because the emboli pass through the circulation and can be found in pulmonary veins within two to four hours

Liquor amnii. This can cause fatal pulmonary embolism. This was shown by Steiner and Lushbaugh in 1941 and up to 1956 there were 64 cases recorded. It is a probable mechanism of death in some cases of obstetric shock. It occurs in cases where very severe uterine contractions occur behind an impacted foetal head and force liquor amnii into the maternal circulation. According to Tuller (1957) it may be a cause of afibrinogenaemia by the release of a thromboplastin-like substance from the placenta into the circulation and the formation of intravascular fibrin thrombi which embolized small vessels throughout the body.

Tumour embolism. This is of course a regular occurrence in the majority of malignant tumours and is probably the usual route of spread of pulmonary metastases. In a very small proportion of cases the involvement of the pulmonary vasculature is sufficient to cause significant obstruction and give rise to signs and symptoms of cor pulmonale and even death (Bagshawe and Brooks, 1959). Such cases of embolic obstruction by tumour are extremely rare but there is a somewhat less rare form in which cancer cells permeate the lungs via the lymphatics producing the condition of so-called lymphangitis carcinomatosa. The tumour cells having formed cuffs around the pulmonary arteries invade them and cause thrombosis. Morgan (1949) has suggested that in some at least of these cases the spread to the lungs was really embolic and that the tumour cells invaded through the wall of the small peripheral arteries and entered the lymphatics in which they were able to spread widely throughout the lungs. It is interesting to note that in three-quarters of the cases of lymphangitis carcinomatosa the primary is in the stomach (Morgan). Whatever is the route of spread the vascular obstruction is mainly due to the thrombosis that accompanies the tumour spread. So much is this so that it is wise to search any case of widespread pulmonary vascular thrombosis in order to exclude tumour as a cause.

Parasitic pulmonary embolism. The only form that is of clinical significance is that caused by the Schistosoma haematobium. In Egypt where schistosomiasis is extremely

common, Shaw and Ghareeb (1938) found that 33 per cent of those infested had pulmonary lesions due to embolism by ova. The latter pierce the walls of the small muscular pulmonary arteries and migrate into the adjacent connective tissue and in doing so cause a fibrous obliteration of the arteriole. In very severe infestations (two per cent of all infestations) the number of arterioles obliterated was sufficient to cause fatal right heart failure, similar infestation occurs in Puerto Rico and due to recent immigration these parasitic pulmonary lesions are now being seen in the U.S.A.

Pulmonary thrombosis. Thrombosis secondary to mitral disease and to hyperkinetic pulmonary hypertension have already been discussed under their appropriate headings. There remains a small group of cases in which major pulmonary thrombosis occurs apart from any apparent cause. Most of these are really cases of pulmonary embolism with secondary overlying thrombosis The distinction is not easy but can usually be made by careful dissection The embolus impacts in a coiled or twisted form but does not occlude enough of the circulation to cause death The embolus soon shrinks, partly relieving the circulation, but it forms a base on which secondary thrombus readily deposits. In so doing the thrombus smooths out the irregular, coiled outlines of the original embolus Meanwhile organization from below fixes the thrombus to the arterial wall In our experience careful dissection is more useful than histology for recognizing emboli with secondary thrombosis Histological examination is of value in recognizing the presence of arterial disease on which local thrombosis can be initiated and the regular laminations in which local thrombi are built up In spite of all care, however, it is not always possible to be sure of the origin of such lesions though we believe that the majority are originally embolic.

OBSTRUCTION TO THE PULMONARY CIRCULATION BY CHANGES IN THE ARTERIAL WALLS

The most common and important example of this group is the intimal proliferation that occurs in small arteries and especially in arterioles in response to severe hypertension. These have already been discussed. In addition there are primary diseases of the walls of pulmonary arteries Of the diseases that affect the systemic arteries most do not affect the pulmonary circulation Buerger's disease and giant cell arteritis are virtually unknown in the pulmonary circulation. Syphilis may affect the lung in the form of gummata or in pneumonia alba of congenital cases but in both of these syphilitic arteritis is incidental to the local lesions and not of significance in itself. Polyarteritis nodosa on the other hand does affect the pulmonary circulation and so does scleroderma.

Polyarteritis Nodosa

Before describing pulmonary involvement in this disease it is well to point out that the presence of fibrinoid necrosis even with an acute cellular infiltration in occasional pulmonary arteries does not justify a diagnosis of polyarteritis nodosa. In states of severe pulmonary hypertension and in the neighbourhood of infarcts, particularly in mitral stenosis, it is not uncommon to find single arteries, usually of the smaller muscular type, with fibrinoid necrosis of their walls and a secondary inflammatory cellular infiltration but usually without a cellular intimal proliferation These lesions are quite isolated and

are not associated with generalized arteritis nor do the patients show any of the signs of generalized disease. In true polyarteritis nodosa the pulmonary circulation is unaffected in the majority of cases. When it is affected the disease tends to follow a different clinical pattern (Rose and Spencer, 1957) In such cases the disease commences with a chronic respiratory illness and often with a chronic granulomatous and ulcerative lesion of the nose or ear. After a variable period more generalized symptoms arise and a blood eosinophilia is often found Death may occur from renal failure or other secondary effects At autopsy the smaller muscular pulmonary arteries are involved and are often surrounded by a granulomatous infiltration, eosinophilic infiltration is common and similar granulomatous lesions are found in other organs. Many of the patients fall into the group described by Wegener (1939) and generally known as Wegener's granulomatosis Although involvement of the pulmonary arteries by polyarteritis is the defining character of this group it is fair to point out that only a limited number of pulmonary arteries need be involved The disease is dominated at first by signs of pulmonary infection, later by signs of systemic illness but there are never clinical signs or symptoms to indicate that the pulmonary vasculature is involved and pulmonary hypertension does not occur

The other systemic disease that may involve the pulmonary vasculature is scleroderma or systemic sclerosis In this disease the lungs are involved in most cases (Piper and Helwig, 1955) The usual lesion is interstitial fibrosis of alveolar walls with bronchiolar dilatation and the formation of clusters of small cysts, one of the forms of so-called honeycomb lung Such fibrous sclerosis naturally interferes with the pulmonary vasculature by destroying vast numbers of small arteries and arterioles In addition, however, the pulmonary vessels themselves may be involved, apparently mainly the arterioles and smallest arteries. These develop a hyaline, acellular intimal thickening that produces luminal narrowing. To what extent these two processes, pulmonary fibrosis and vascular sclerosis, are severally or jointly responsible for the pulmonary hypertension that not infrequently occurs is difficult to decide We have, however, studied one case in whom there was evidence of pulmonary hypertension whose lungs were free from fibrosis but showed hyaline thickening of pulmonary arterioles.

PULMONARY HYPERTENSION DUE TO VASCULAR OBSTRUCTION BY LESIONS OF THE LUNG PARENCHYMA

Under this heading there are two groups of lesions, those characterized by pulmonary fibrosis and those characterized by emphysema

Pulmonary Fibrosis

In this group the most important is pneumoconiosis, comprising silicosis, asbestosis and coal-miners' lung

In silicosis the fibrous nodules or confluent areas of fibrosis are associated with fibrous endarteritis of the pulmonary arteries lying within them and often destruction of the media as well. So much is this so that over extensive areas of lung it is often difficult to find pulmonary arteries except by staining for elastic tissue, when the collapsed elastic laminae can be recognized. If, as so often happens, silicosis is complicated by tuberculosis the

degree of vascular obliteration is still further increased. Quite apart from any pulmonary hypertension that may be induced by failure of gaseous exchange, the total vascular territory obliterated by fibrosis may be sufficient to cause simple obstructive pulmonary hypertension with cor pulmonale. Essentially the same is true of asbestosis, although the type and distribution of the fibrosis is different.

Miners' pneumoconiosis takes two forms. The simple, uncomplicated lesions consist of an accumulation of coal dust around the respiratory bronchioles with localized lung destruction giving a picture of centrilobular emphysema. In this form of the disease the pulmonary arteries are not much involved and the effect of the lesions on the pulmonary circulation is simply the effect of the accompanying emphysema. So far as the pulmonary circulation is concerned, the far more important lesion is complicated pneumoconiosis or progressive massive fibrosis. In this disease large rounded foci of lung tissue, several centimetres in diameter, undergo dense fibrosis with the incarceration of masses of coal dust producing round, black lesions, often of extreme hardness. There is now good circumstantial evidence to indicate that progressive massive fibrosis (P.M.F.) is due to an altered form of chronic tuberculosis occurring in a dust-laden lung: a condition analogous to that seen in silico-tuberculosis. In practice, miners affected with this condition ordinarily die of cor pulmonale and Wells (1954) has shown by angiographic studies that the anatomical basis for this is a widespread fibrous obliteration of pulmonary vasculature similar to that seen in silicosis. Apart from pneumoconiosis, it is unusual for any form of pulmonary fibrosis to lead to sufficient vascular obliteration to produce pulmonary hypertension.

Emphysema

The usual effect of emphysema is to produce cor pulmonale, but there is very little evidence to suggest that the mechanism is one of vascular obstruction. The physiological effects of emphysema are dealt with elsewhere, it suffices here to discuss the structural changes. In angiographs of emphysematous lungs the larger arteries are if anything a little dilated and the smaller arteries can be traced down to quite fine branches without any apparent loss of vascular territory. What loss there is lies in the territory of the arterioles and alveolar capillaries and in the latter there is an undoubted loss. Nevertheless it is questionable whether this affects the vascular capacity sufficiently for obstruction to play a significant part in the production of hypertension. There is not as a rule any significant disease in the arteries or arterioles leading to emphysematous areas and in injected specimens well-filled arterioles can be seen traversing empty spaces.

PULMONARY HYPERTENSION DUE TO VASCULAR CONSTRICTION

Pulmonary arterial constriction occurs as a secondary event in passive pulmonary hypertension if it is of more than mild degree and it is the dominant mechanism in mitral stenosis. Similarly in hyperkinetic pulmonary hypertension the increased pulmonary vascular resistance is due to increased vascular tonus at least at first. Finally, increased pulmonary vascular tonus is excited by hypoxia and locally by pulmonary collapse. The problem arises, does increased pulmonary vascular tonus occur as a primary event? If so, such cases would constitute true examples of idiopathic pulmonary hypertension.

Obviously such a diagnosis can only be sustained if all the known causes of pulmonary hypertension can be excluded. Such an exclusion can only be presumptive during life and needs great care at autopsy. When the more obvious causes have been excluded the problem remains whether the individual case could have been due to showers of minute emboli occluding sufficient vessels to cause organic obstruction. It has been shown experimentally (Harrison, 1948) that this is possible and that such emboli become incorporated into the arterial wall to produce lesions greatly resembling natural arterial disease. In man there are numerous recorded cases (Castleman and Bland, 1946) of fatal cor pulmonale apparently due to such micro-embolism. Naturally this possibility has to be excluded in every case and since the arterial lesions so produced resemble those of hypertensive arterial disease it is possible to regard virtually every case with any intimal thickening as due to healed embolism, and some workers seriously question whether idiopathic pulmonary hypertension exists as a real entity. Cases could presumably be accepted if they

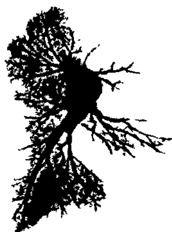


FIG [illegible] branches are greatly narrowed

had all the clinical and physiological signs in life and if at autopsy the only finding was pure hypertrophy of the pulmonary arterial tree. In practice, by the time death occurs the affected arteries show serious intimal lesions and in fact it is always a matter of interpretation whether any given case can be accepted as idiopathic or not. We would suggest that in trying to assess what sort of intimal changes can be accepted as resulting from a hypothetical idiopathic pulmonary hypertension one might take for comparison those changes that are seen in cases of ventricular septal defect or patent ductus. In these two conditions the pulmonary vasculature is in a state of tonic constriction, exerting a high vascular resistance and the resultant pulmonary arterial pressure is of the same order as that recorded in cases of presumptive idiopathic pulmonary hypertension. There is no valid reason for doubting that in cases of ventricular septal defect the arterial changes are the result of the hypertension, and that this hypertension is the result of the vascular resistance

degree of vascular obliteration is still further increased. Quite apart from any pulmonary hypertension that may be induced by failure of gaseous exchange, the total vascular territory obliterated by fibrosis may be sufficient to cause simple obstructive pulmonary hypertension with cor pulmonale. Essentially the same is true of asbestosis, although the type and distribution of the fibrosis is different.

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intense local spasm. A constant finding is the presence of fibrous or sometimes fibro-elastic intimal thickening leading to narrowing or even obliteration of the lumen. In many vessels this is concentric and analagous to the change seen in small arteries in severe systemic hypertension. In other cases, the thickening is eccentric and appears to result from the organization of minute foci of thrombosis. Serial section studies show that these lesions are often focal along the length of the artery. The glomerulus-like structures described in hyperkinetic pulmonary hypertension are also seen. Pulmonary capillaries, veins and lung parenchyma show no constant or significant lesions. It will be seen that the changes described above are very similar to those seen in hyperkinetic pulmonary hypertension due to ventricular septal defect with the exception of the pattern of elastic hypertrophy. This is not surprising because we believe that in many ways the vascular response is similar in these two conditions

VASCULAR CHANGES IN PULMONARY OLIGAEMIA

The structural effects on the pulmonary vasculature of the different forms of pulmonary stenosis depend upon the pressure and flow in the pulmonary arteries rather than on the particular combination of anatomical lesions responsible. Thus in the Tetralogy of Fallot it is possible to have the ventricular septal defect and over-riding aorta combined with a relatively mild pulmonary stenosis so that the net effect is pulmonary hypertension. In such cases the pulmonary vasculature shows the usual response to hypertension. In other cases the pulmonary arterial pressure and flow may be within normal limits and cause no changes in the arterial structure. The effect in most cases of the Tetralogy of Fallot and in all cases of isolated pulmonary stenosis is a diminished pressure and flow in the pulmonary arterial system. If the pulmonary stenosis is valvular, post-stenotic dilatation of the main pulmonary arteries is usual, if the stenosis is infundibular no such dilatation is seen. Beyond the main pulmonary artery there is no dilatation seen in life and radiographs usually show translucent oligaemic lung fields. This must be due to a lack of filling pressure because anatomically there is no diminution in the size of the intrinsic pulmonary arteries In fact, we have noted that such lungs, when injected at autopsy, tend to have slight arterial dilatation at the level of both the elastic and muscular arteries. This may be artefactual due to overdistension of thin-walled arteries but we have noted a similar apparent enlargement in histological sections of uninjected lungs It is certainly safe to say that there is no narrowing in the elastic or larger muscular arteries. Structurally there appears to be some thinning of the media of these vessels but since the estimation of medial thickness is so difficult it is not possible to make any definite statement on this point. In the case of the main pulmonary artery, it is possible to make reliable measurements and here it has been shown that in pulmonary hypotension the wall is half to two-thirds of normal thickness and the elastic tissue is atrophic. In some cases of pulmonary stenosis peculiar focal vascular obstructions are seen. These were originally described by Rich in 1948 and occur in the small ([illegible]

there is gross dilatation of adjacent vessels producing a cluster of irregular thin-walled channels that resemble a cavernous angioma. Rich showed that these lesions were due to

excited by tonically contracted arteries and arterioles against the outflow from the combined ventricles It seems logical to assume that if similar vascular constriction occurred as a primary event it might produce similar arterial and arteriolar lesions These are the reasons that we consider justify us in accepting a certain limited number of cases as examples of idiopathic pulmonary hypertension (Wade and Ball, 1957). Because of these difficulties in deciding what cases are acceptable as examples of idiopathic pulmonary hypertension it follows that a description of the pathological findings must be to a large extent based on personal opinion. Macroscopically the lungs are free from congestion and oedema and the only change visible is likely to be premature atheroma of the main pulmonary arteries. Angiograms usually show dilatation of mild degree in the arteries down

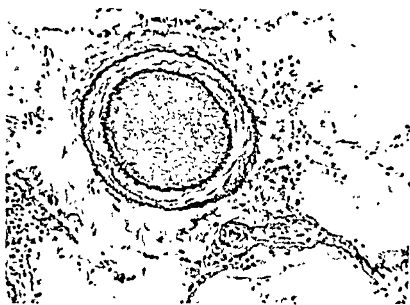


FIG 69 Idiopathic pulmonary hypertension Same case as Fig 68 A muscular pulmonary artery shows marked hypertrophy, the adjacent arteriole shows fibrous intimal thickening (elastic stain ×225)

to about the level of segmental arteries. The latter and their branches are likely to be about normal-sized. Beyond the elastic arteries there is a striking lack of filling due to narrowing and occlusion of muscular arteries so that the angiogram has a bare, empty, appearance (Fig 68)

Histologically the elastic arteries may show premature atheroma but since most of the patients are young women this is not a striking or constant change. There is hypertrophy in elastic arteries and we have observed the acquired type of elastic type of hyperplasia described by Heath *et al.* (1958b) The striking and constant changes occur in the muscular arteries and the arterioles. The former show muscular hypertrophy (Fig. 69), the latter, which normally have muscle only at their origins, become muscular to a more distal level. In muscular arteries focal medial scarring with loss of muscle and elastic may be found This probably results from focal necrosis that is not infrequently seen and is strictly limited to small lengths of artery. The origin of the necrosis is unknown but it might result from

enter the bronchial arteries and flows in sufficient volume to leak out of the cut ends of the bronchial arteries and necessitate tying off. Such enlarged bronchial arteries may have a diameter of about 1–2 mm. The main site of anastomosis between pulmonary and bronchial systems is via very thick-walled arteries ("sperrarterien") at the level of the distal cartilaginous bronchi (Verloop, 1948). Further anastomoses occur between bronchial arteries running in the subpleural layer and the distal pulmonary arteries.

With complete failure of development of the pulmonary arteries, the bronchial arteries take over the circulation in the lungs. We have had the opportunity of studying one such

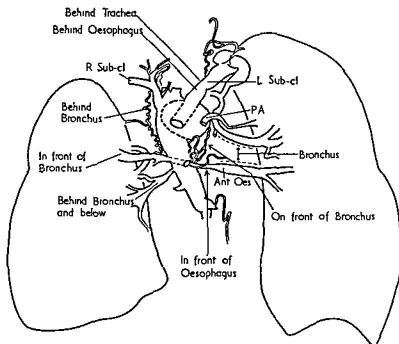


FIG 71. Pulmonary atresia Tracing of a post-mortem angiogram The

case in a child of 14 with tricuspid atresia and a minute pulmonary artery with a blind proximal end. The whole pulmonary circulation was supplied by greatly enlarged bronchial arteries, the anatomy of which is shown in Fig. 71.

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local thrombosis, that they occurred at ages from infancy up to adult life and were present in 19 out of a series of 21 fatal cases of the Tetralogy of Fallot. He postulated that they were due to a combination of slow flow and polycythaemia and postulated that they were liable to vitiate the expected benefits of cardiac surgery. Rich's findings have since been confirmed, and extended. Heath *et al.* (1958) have confirmed that these lesions depend on a low pulmonary blood flow and a polycythaemia irrespective of whether the cause is a Tetralogy of Fallot or an isolated pulmonary stenosis They found them to be less frequent in children under ten years although this conflicts with Rich who found 16 of his 19 positive cases in children of less than ten years. Whether these lesions are clinically significant depends on their number. Since each lesion represents an obstruction at a



FIG 70 Pulmonary stenosis Small pulmonary artery showing organized thrombosis with multiple new channels (elastic stain ×225)

peripheral level sufficient could produce organic vascular obstruction but clearly at this level in pulmonary vasculature the number of such lesions would have to be very great. In fact these obstructive lesions can be extremely numerous and when allowance is made for the fact that a single focus in the length of an artery is sufficient to cause an impediment to its flow, the number visible in a random section will be far fewer than the number of arteries actually obstructed In fact there is evidence that these minute thrombotic lesions are clinically important and that disappointing results after surgical intervention can be attributed to them.

With a diminution of pulmonary artery blood flow the flow via the bronchial arteries increases and these vessels enlarge. This enlargement is not enough to be obvious to even apparent on routine anatomical dissection. It does become apparent if the lungs are injected via the pulmonary arteries. Ordinarily masses injected into the pulmonary artery do not enter the bronchial system. In cases of pulmonary stenosis, however, the mass does

CHAPTER 7

ELECTROCARDIOGRAPHY

BY JOHN GOODWIN

THE electrocardiogram is affected by disorders of the pulmonary circulation which produce changes in atrial and ventricular function, especially those of the right ventricle.

Before considering electrocardiographic abnormalities due to lesions of the pulmonary circulation it is necessary to give a brief and simplified description of the normal cardiogram and its genesis.

The normal cardiogram reflects the balance of electrical forces acting on the atria and ventricles during the period of contraction, during which time the muscle becomes depolarized. At any given moment, the sum of all the forces has magnitude and direction and is known as the vector There is a vector for atrial depolarization (P vector), for ventricular depolarization (QRS vector) and for repolarization (T vector) The projection of each vector upon the horizontal and frontal planes can be recorded as a loop by vectorcardiographic techniques

As the normal left ventricular wall is three times as thick as the right, the left ventricle dominates the right ventricle in the normal cardiogram.

The normal vectorcardiogram is orientated to the left, inferiorly and posteriorly. In the horizontal projection the normal QRS loop has a small initial deflection anteriorly to the right, and this is followed by the remainder of the loop, which is inscribed in a counter clockwise direction to the left and slightly posteriorly. The left ventricle dominates the vector forces, and this results in small positive deflections over the right praecordium and large positive deflections over the left praecordium The former are the result principally of right, and the latter of left ventricular, forces

In the frontal plane the normal QRS loop is inscribed downward and to the left The angle which the mean vector makes with the horizontal is known as the cardiac axis

The conventional scalar cardiogram records the projection of the vector loop on the frontal and horizontal planes

The normal cardiac axis lies between 0 and 90 degrees, all three limb leads showing dominant R waves Slight or moderate degrees of axis deviation to left or right are compatible with normality. The unipolar limb leads reflect the projection of the vector from the centre of the heart on a direct line to the lead concerned, whereas the bipolar standard leads reflect the projection of the vector merely in the axis of that lead Unipolar leads therefore give a truer idea of the balance of forces at any one point than do bipolar leads

The normal adult cardiogram is shown in Fig 72, mounted with the praecordial leads, (representing the horizontal vector), in the centre, and the limb leads, (representing the frontal vector), arranged around (Wood, 1956) Lead V4R, placed to the right of the

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[illegible] y hypertension *Quart J Med*, 26, 83
[illegible] Granulomatose mit besonderer Beteiligunge des
[illegible], 102, 36
[illegible] -workers' pneumoconiosis *J. Path Bact.*, 68, 573
[illegible] Patent ductus arteriosus with pulmonary hyper-
[illegible]

pulmonale (Mounsey *et al.*, 1952), or in congenital heart disease with left to right shunt, notably atrial septal defect. Cabrera and Monroy (1952) have divided the patterns of ventricular hypertrophy into "systolic overload" and "diastolic overload". The former refers to situations, such as lone pulmonary stenosis, in which the ventricle is working against resistance alone (pressure work), and is typified by tall R waves, and often inverted T waves over the right praecordium. The latter indicates a ventricle which is dilated, as well as hypertrophied, owing to a left to right shunt and increased pulmonary blood flow. In this type, right bundle branch block, partial or complete, may not be accompanied by dominant right praecordial R waves

The distinction is a useful one, and often helps to suggest the diagnosis from the cardiogram.

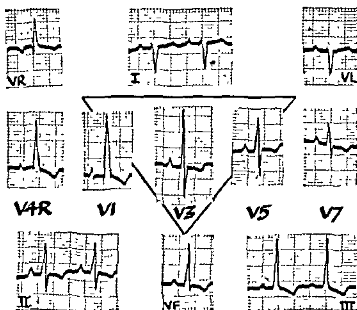


Fig 73 Gross right ventricular, and right atrial, hypertrophy Female 26 years

The P wave reflects atrial electrical forces, and when tall and peaked, suggests right atrial enlargement or rotation (Fig. 73). The upper limit of normal height for adults is 2·5 mm. but the shape of the P wave is often a guide in borderline cases When left atrial enlargement is present the P wave broadens, and becomes notched When enlargement of both atria is present, the first peak of the P wave dominates the second Sometimes the PR interval is prolonged.

The Influence of Age upon the Cardiogram

In foetal life the right ventricle dominates the left, as a result of the extreme pulmonary vascular resistance (Chapter 9). In infancy this situation persists while the pulmonary resistance falls to normal, and while the right ventricle gradually involutes to the stage at

sternum in a position analogous to that of V4 to the left of the sternum, is an important additional lead in the detection of right ventricular hypertrophy, and should be used routinely (Camerini *et al.*, 1956). Lead VR is normally a totally negative lead and a dominant positive deflection indicates right ventricular hypertrophy if certain forms of cardiac infarction and cardiac aneurysm are excluded.

Right Ventricular Hypertrophy

Signs of right ventricular hypertrophy will appear when the right ventricle enlarges sufficiently to disturb the normal ventricular balance, so that the QRS vector loop is rotated to the right In addition the loop is rotated anteriorly and inferiorly in mild

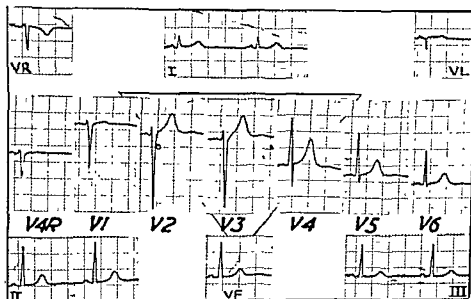


FIG 72 Normal adult cardiogram Male aged 31 years

degrees, anteriorly and superiorly in moderate degrees, and posteriorly and superiorly in severe degrees, of right ventricular hypertrophy (Grishman *et al.*, 1953)

This rotation results in the appearance of dominant R waves in right praecordial leads, a strongly vertical heart position (right axis deviation), a deep S wave in lead V5 and often a dominant R wave in lead VR (Sokolow and Lyon, 1949; Myers *et al.*, 1948) (Fig 73). There is often a q wave preceding the large R wave in right praecordial leads in extreme right ventricular hypertrophy. Its origin is not known, but it may be due to interference [illegible] normal septal activation from left to right (Fowler *et al* , 1952), or to normal [illegible] dial leads. [illegible] in a plane parallel to that of the lead (Camerini *et al* , 1956)

In many cases of right ventricular enlargement, some form of right bundle branch block is present. This may arise secondarily to extreme hypertrophy, when the secondary R wave towers above the initial r wave. But often it is seen in the early stages of cor

Delay in the intrinsicoid deflection, due to prolonged activation time, is usually present in right praecordial leads in pathological right ventricular hypertrophy but has not proved of value in diagnosis.

The electrical axis of the heart is usually strongly deviated to the right, and may be of value in diagnosis. An abnormal degree of right axis deviation was found in 55 per cent of Hollman's cases of pathological right ventricular hypertrophy The P wave should not normally exceed 3 mm. in height in lead II in children (Table 5)

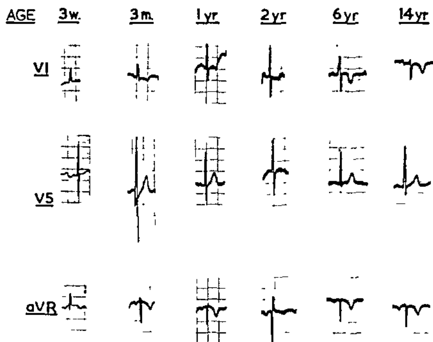


FIG 74 Leads VI, V5 and VR in normal children from 3 weeks to 14 years (From Hollman, (1958) *Brit Heart J*, 20, 129 Reproduced by courtesy of the Editor, *British Heart Journal*)

Ziegler (1956) has shown that the T waves are normally positive in right praecordial leads only during the first 24 hours of life. He considers that the presence of positive T waves in these leads after the first 24 hours may suggest pathological right ventricular hypertrophy, especially if there is evidence of left hypertrophy and if the amplitude of R in VI equals or exceeds 50 per cent of the total amplitude in that lead

The Contribution of Cardiography to Assessment of the Pulmonary Circulation

The cardiogram reflects enlargement of the right ventricle and atrium, whether acute or chronic, and in general will not give information as to the cause. For example, the cardiogram of pulmonary stenosis and pulmonary hypertension of severe degree may be

which the normal relation to the left ventricle is reached As would be expected, the cardiogram at birth shows marked right ventricular dominance, and this gradually regresses, until the normal adult ventricular balance is reached at about 13 years of age.

The criteria for the diagnosis of pathological degrees of right ventricular hypertrophy in infancy and childhood have been laid down by Hollman (1958). These criteria are of the greatest importance for the differential diagnosis of pathological from physiological hypertrophy in the early days of life (Fig. 74) (Table 5)

TABLE 5

CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY FROM ONE MONTH TO FIFTEEN YEARS OF AGE

(1) Presence of a Q wave in V1.
(2) Onset of intrinsicoid deflection in V1 delayed to 0 04 sec or more in the absence of right bundle branch block
(3) R/S or R/Q in a VR of over 1 0
(4) P wave of 3 mm or more in lead II, or 2 5 mm. or more in any other lead
(5) Electrical axis of over +120°
(6) R/S in V1 and V5 as below.

	1–3 *months*	4–11 *months*	1–2 *years*	3–5 *years*	6–15 *years*
R/S V1	7 0	4 5	2 5	2 0	1 5 or more
R/S V5	0 5	0 7	0 8	0 9	0 9 or less

From Hollman (1958).

The most difficult diagnostic period is under one year, and Hollman has stressed the value of lead V5 since there is little overlap between the normal and abnormal R/S ratios in this lead. In the normal infant the R/S ratio in V5 is always 0·6 or more, whereas pathological right ventricular hypertrophy almost invariably produces a ratio of less than this in infants, including those under three months of age In lead V1 there is definite overlap between the physiological and pathological under the age of three months. It is important to consider more than one lead and the diagnosis can best be made from a combined study of leads V1, V5 and VR. No information is available on the value of V4R in infancy The presence of a q wave in V1 indicates pathological hypertrophy in infants over the age of one month (Table 5).

Lead VR has been shown to be of importance in the diagnosis of pathological degrees of right ventricular hypertrophy in childhood. A dominant R in VR was found in 83 per cent of a personal series of 36 cases of right ventricular hypertrophy due to congenital heart disease in children between the ages of 3 to 14 years. The dominant R wave in VR was never seen in normal children at this age, and was of particular value in pathological cases in which the r wave was not dominant in V1 Absence of a dominant R in VR, however, does not exclude pathological right ventricular hypertrophy (Goodwin, 1952)

Lead VR also is of value in infants down to the age of one month, as shown by Hollman Under the age of one month this lead shows a dominant R wave and differential diagnosis of physiological from pathological hypertrophy may be virtually impossible in the first four weeks of life, except perhaps from the R/S ratio in lead V5 (Fig. 74).

The cardiogram changes rapidly in the first weeks of life, and serial tracings at weekly intervals are of great value in diagnosis, for in abnormal cases the signs of right ventricular hypertrophy become more, instead of less, obvious and diagnosis may be possible after the age of eight to ten weeks.

Delay in the intrinsicoid deflection, due to prolonged activation time, is usually present in right praecordial leads in pathological right ventricular hypertrophy but has not proved of value in diagnosis.

The electrical axis of the heart is usually strongly deviated to the right, and may be of value in diagnosis. An abnormal degree of right axis deviation was found in 55 per cent of Hollman's cases of pathological right ventricular hypertrophy The P wave should not normally exceed 3 mm. in height in lead II in children (Table 5)

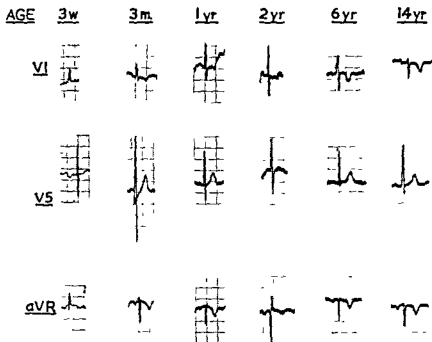


FIG 74 Leads V1, V5 and VR in normal children from 3 weeks to 14 years. (From Hollman, (1958) *Brit Heart J*, 20, 129 Reproduced by courtesy of the Editor, *British Heart Journal*)

Ziegler (1956) has shown that the T waves are normally positive in right praecordial leads only during the first 24 hours of life He considers that the presence of positive T waves in these leads after the first 24 hours may suggest pathological right ventricular hypertrophy, especially if there is evidence of left hypertrophy and if the amplitude of R in V1 equals or exceeds 50 per cent of the total amplitude in that lead

The Contribution of Cardiography to Assessment of the Pulmonary Circulation

The cardiogram reflects enlargement of the right ventricle and atrium, whether acute or chronic, and in general will not give information as to the cause. For example, the cardiogram of pulmonary stenosis and pulmonary hypertension of severe degree may be

identical, because the medium by which they produce cardiographic changes (enlargement of the right ventricle) is common to both.

Nevertheless, various individual cardiac lesions have characteristic cardiograms, and the diagnosis may often be suggested by the type or degree of right ventricular hypertrophy present, and by certain associated abnormalities.

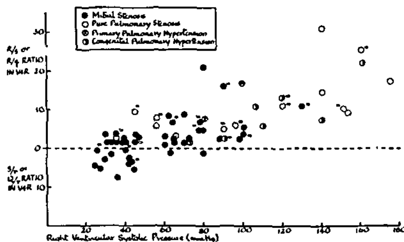


FIG 75*a*

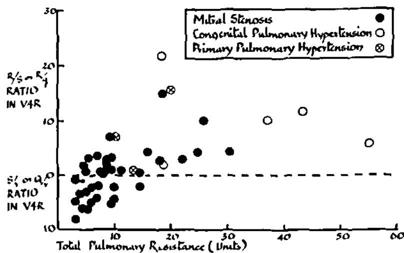


FIG. 75*b*

Before considering the cardiogram in individual disorders, a method of grading the severity of right ventricular hypertrophy from the ventricular complex of the cardiogram will be discussed (Goodwin and Abdin, 1959).

The grades are as follows:

Grade 1. Dominant R wave in lead V4R or dominant S in V5.

Grade 2. Dominant R wave in V4R and V1 or dominant R in V4R, with dominant S in V5 or R in VR.

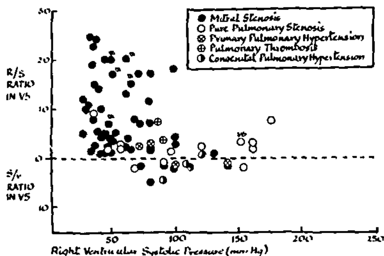


FIG 75*c*

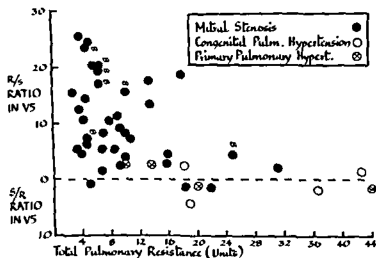


FIG 75*d*

Fig 75

(*a*) R/S ratio in V4R or V1, and right ventricular systolic pressure (Correlation coefficient = 0·76)

(*b*) R/S ratio in V4R or V1 and total pulmonary vascular resistance. (Correlation coefficient = 0 46)

(*c*) R/S ratio in V5 and right ventricular systolic pressure (Correlation coefficient = −0 45)

(*d*) R/S ratio in V5 and total pulmonary vascular resistance (Correlation coefficient = −0 55)

Grade 3. Dominant R in V4R, V1 and VR, with dominant S in V5.

Grade 4 Dominant or monophasic R in V4R of 10 mm. or more, with or without qR pattern, dominant R in V1; dominant S in V5; with or without dominant R in VR, and T inversion in right praecordial leads.

This system of grading covers most cases, but some will inevitably fail to fall clearly into a grade, in view of the number of variable signs involved. A dominant S wave in V5 without a dominant R in V4R or V1 has been shown to mask an old anterior infarction (Goodwin, 1958), but may also occur with lone right ventricular hypertrophy. P waves indicating right atrial enlargement contribute a valuable indirect sign of right ventricular hypertrophy, but usually only when other signs are present, and is therefore not included in the grading system.

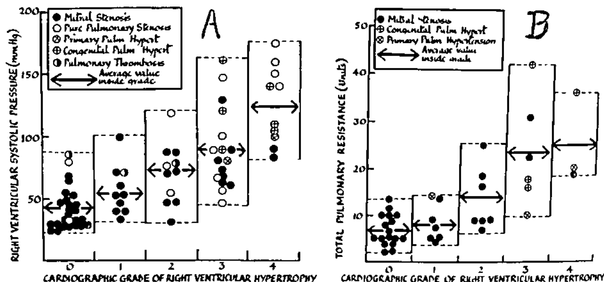


FIG 76 Cardiographic grade of right ventricular hypertrophy and (*A*) right ventricular systolic pressure, and (*B*) total pulmonary vascular resistance. Each dot represents one case.

Haemodynamic and pathological factors. Cosby *et al* (1952, 1953) compared right ventricular pressure, flow and work, with the cardiographic evidence of right ventricular hypertrophy, and noted a positive correlation. This was also shown by Goodwin and Abdin (1959). Fig 75 shows the relationship of signs of right ventricular hypertrophy in V4R and V5 to total pulmonary vascular resistance (TPR) and right ventricular systolic pressure (RVSP) respectively, in various disorders causing right ventricular hypertrophy. There is a positive correlation with a dominant R wave in V4R and with a dominant S wave in V5 with both TPR and RVSP. Total pulmonary vascular resistance is calculated by dividing the mean pulmonary artery pressure by the cardiac output, the maximum normal being regarded as four units. A positive trend is also found between the severity of right ventricular hypertrophy and the RVSP and TPR (Figs 76 and 77).

These comparisons show that the cardiographic changes are largely determined by the load imposed on the right ventricle by obstruction to flow at the outflow tract or pulmonary arteriolar level. They do not take account of "diastolic overload" patterns, since

cases with bundle branch block were deliberately excluded from the series in view of the difficulty of assessing associated right ventricular hypertrophy.

There is also an association between right ventricular hypertrophy assessed cardiographically, and the ratio of thickness of right and left ventricles (RV/LV ratio). In 28

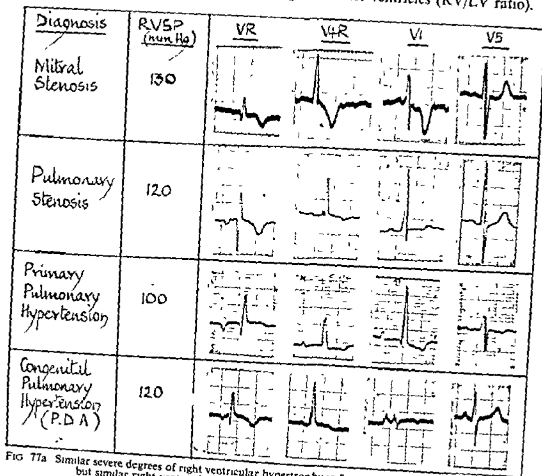


FIG 77a Similar severe degrees of right ventricular hypertrophy in four patients with different disorders but similar right ventricular pressures (RVSP) (PDA = patent ductus arteriosus)

cases there was a significant correlation between the R/S ratio in V4R and the RV/LV thickness ratio (Goodwin and Abdin, 1959).

Therefore, as would be expected, the anatomical degree of hypertrophy which is the consequence of the right ventricular hypertension also correlates with the cardiogram

These associations may only be expected to remain valid in the absence of bundle branch block, definite left ventricular hypertrophy, or other myocardial disease

The Cardiogram at high altitudes

altitu... ...dents at high tension and positional changes

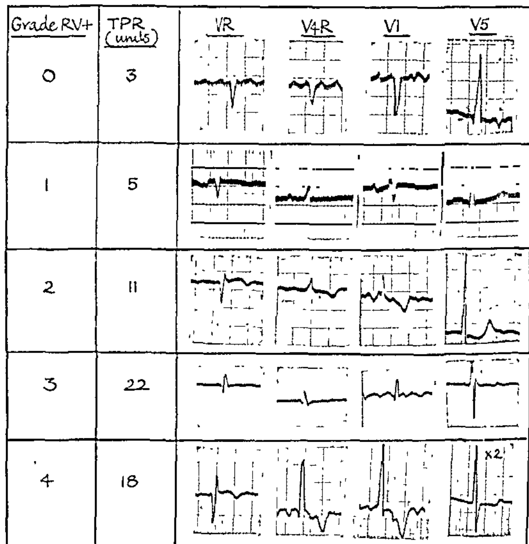


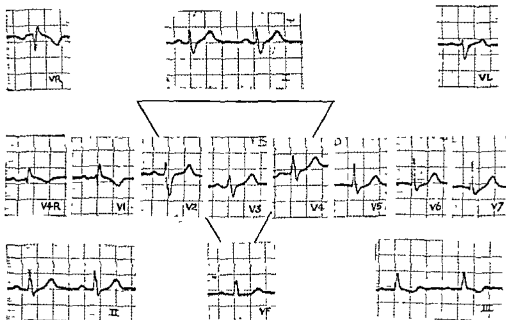
FIG 77b Increasing grades of right ventricular hypertrophy with increasing total pulmonary resistance in five patients with mitral stenosis (TPR = total pulmonary vascular resistance)

THE CARDIOGRAM IN SPECIFIC CARDIOPULMONARY DISORDERS

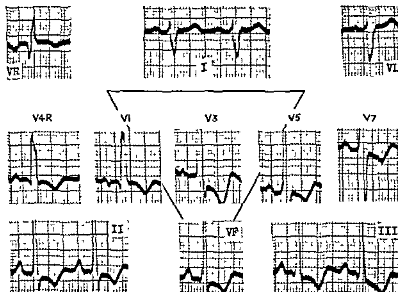
1. Congenital Heart Disease

Conditions with increased pulmonary blood flow

Atrial septal defect. Right bundle branch block is present in some form in the majority of cases, but is often "incomplete", with an rSr′ complex in right praecordial leads, (with normal QRS duration), and an S wave in V5. The presence of large secondary R waves or Q waves in V4R and V1 suggests right ventricular hypertrophy in addition, and may indicate either pulmonary stenosis, or severe pulmonary hypertension. There is usually right axis deviation (Fig. 78).



(*a*)



(*b*)

FIG 78. Atrial septal defect: (*a*) without increased pulmonary vascular resistance, (*b*) with raised pulmonary vascular resistance and reversed shunt (Eisenmenger Reaction)

Note the complete right bundle branch block in both, and the tall R waves in right praecordial leads with q wave indicating severe right ventricular hypertrophy in (*b*)

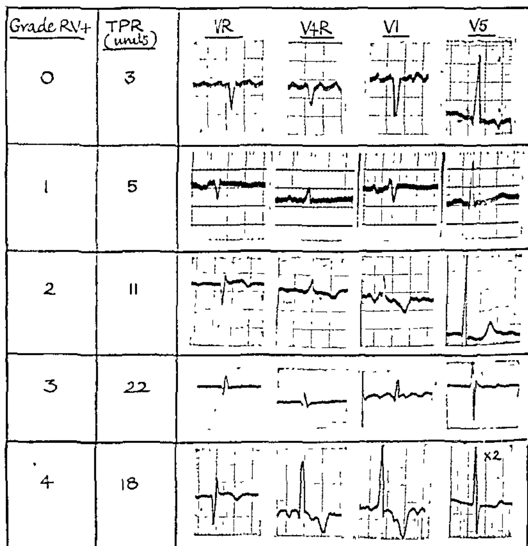


FIG 77b Increasing grades of right ventricular hypertrophy with increasing total pulmonary resistance in five patients with mitral stenosis (TPR = total pulmonary vascular resistance)

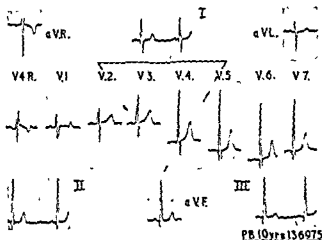
THE CARDIOGRAM IN SPECIFIC CARDIOPULMONARY DISORDERS

1. Congenital Heart Disease

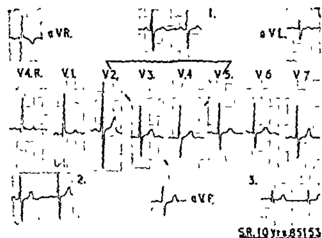
Conditions with increased pulmonary blood flow

Atrial septal defect. Right bundle branch block is present in some form in the majority of cases, but is often "incomplete", with an rSr′ complex in right praecordial leads, (with normal QRS duration), and an S wave in V5. The presence of large secondary R waves or Q waves in V4R and V1 suggests right ventricular hypertrophy *in addition, and may* indicate either pulmonary stenosis, or severe pulmonary hypertension. There is usually right axis deviation (Fig. 78).

with a large left to right shunt (diastolic overload of the left ventricle). Some evidence of right ventricular hypertrophy is usually present, while atrial hypertrophy may be seen in



(a)



(b)

FIG 80 Ventricular septal defect.

(a) With large left to right shunt and low pulmonary resistance. Note peaked T waves, q waves and tall R waves in left praecordial leads.

(b) With high pulmonary arteriolar resistance (9 units), and smaller left to right shunt. Note marked right ventricular hypertrophy with no evidence of left ventricular hypertrophy

some cases. When pulmonary hypertension is appreciable, marked right ventricular hypertrophy is seen, and incomplete right bundle branch block may occur. It might be anticipated that in the presence of dominant left hypertrophy the pulmonary flow would be

The bundle branch block pattern is thought to be due to the dilatation of the right ventricle which occurs as a result of the left to right shunt.

Walker *et al.* (1956) have suggested that the rSr′ patterns in right praecordial leads represents selective hypertrophy of the basal portion of the right ventricle secondary to its increased stroke volume. The complication of pulmonary hypertension causes hypertrophy of the free wall of the right ventricle and produces a dominant R wave. This concept is similar to that of systolic and diastolic overload, introduced by Cabrera and

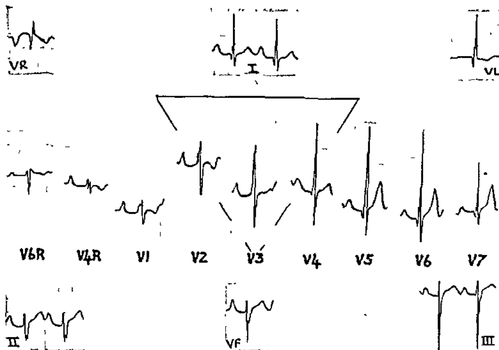


FIG 79 Ostium primum atrial septal defect, atrioventricular canal. Note right bundle branch block, q waves in left praecordial leads, left axis deviation, long PR interval and right atrial enlargement

Monroy (1952). The QRS vector loop is rotated clockwise, to the right, inferiorly and anteriorly (Burch and De Pasquale, 1959)

When an atrial septal defect is of the ostium primum type, with partial or total atrioventricular canal, the cardiogram presents characteristic features which are of great value in diagnosis Right bundle branch block, complete or incomplete, is combined with left axis deviation and a prolonged PR interval (Fig. 79) The QRS loop is rotated anticlockwise, to the left, superiorly and posteriorly (Burch and De Pasquale, 1959). Severe pulmonary hypertension is often present, and this may be reflected in tall dominant R waves in right praecordial leads

Ventricular septal defect. In small defects, the cardiogram may be normal. With larger ones, there is usually some evidence of left ventricular enlargement, shown by tall R waves over the left praecordium, prominent Q waves and pointed tall T waves Deep Q waves and sharply pointed T waves are more common when the pulmonary vascular resistance is less than seven units (Bentall *et al.*, 1959). This pattern is usually associated

Transposition of the great vessels. Severe right ventricular hypertrophy is usually present, and there are generally no special features, except in corrected transposition when a deep q wave is seen in right praecordial leads, with a q wave in leads II and VF, and an R/S pattern in left praecordial leads. There may be complete or partial atrioventricular block (Fig. 83c).

Conditions with reduced pulmonary blood flow

Tetralogy of Fallot. The Tetralogy of Fallot usually produces moderate or severe (grades three to four) degrees of hypertrophy, but in a minority of cases only grade two is present. T wave inversion in right praecordial leads which often occurs in severe lone pulmonary stenosis, is seldom seen. In some cases, a dominant R wave is absent in V4R and V1, and the evidence consists only of a deep S in V5, a dominant R in VR, or extreme right axis deviation. Right atrial P waves are rarely present, and right bundle branch block does not occur (Fig 82a).

Lone pulmonary stenosis with normal aortic root. The severity of the stenosis determines the severity of the cardiogram. When the right ventricular systolic pressure exceeds [illegible] lial leads. [illegible] suggest- [illegible] rsion is a useful sign of diastolic hypertension in the right ventricle, although Cabrera and Monroy (1952) regard T inversion as part of the systolic overload pattern. Certainly, T inversion if pronounced is a valuable sign of dangerous right ventricular overload, and indicates that the pulmonary stenosis requires surgical relief T wave inversion is sometimes variable, and inverted T waves may temporarily become positive. The significance of this is uncertain, but lability of the T wave might suggest a small area of myocardial necrosis resulting from reduced coronary artery flow due to a low cardiac output. When the right ventricular systolic pressure is around 100 mm Hg, T inversion is not usually found, and the cardiogram resembles that found in the Tetralogy. This is understandable, for the right ventricular systolic pressure in the Tetralogy seldom if ever exceeds the left, and clinical right ventricular congestive failure rarely occurs.

When pressures are between 50 and 100 mm. Hg, the cardiogram shows milder grades of right ventricular hypertrophy. Sometimes deceptively minor grades occur with severe stenosis, and the cardiogram should not be used to infer that stenosis is slight, although conversely a grade four cardiogram guarantees severe stenosis Right atrial P waves similarly indicate severe stenosis, but are often absent.

Rarer conditions with reduced pulmonary blood flow (*Tricuspid atresia*, *Single ventricle*; *Ebstein's syndrome*) These three conditions will be mentioned because the cardiogram has certain characteristic features which are helpful in diagnosis

In tricuspid atresia the cardiogram is highly suggestive, since it shows left axis deviation, complete lack of any right ventricular hypertrophy, with normal or excessive left ventricular dominance, in a patient with a right to left shunt. Right atrial P waves may occur, and these, combined with evidence of left ventricular hypertrophy, should always arouse the suspicion that the right ventricle is nonfunctional or hypoplastic (Fig. 83a).

Single ventricle may be associated with a left to right shunt and increased pulmonary blood flow. More frequently, a single ventricle is associated with hypoplasia of the right

higher and the pulmonary resistance lower than when the right ventricle dominates the left, but there is not necessarily any strict relationship between cardiographic and haemodynamic events. Indeed, the R/S ratio in lead V1 may decrease as the resistance increases: the opposite of what would be expected This paradoxical finding may have been due to the associated left ventricular enlargement. Nor does the cardiogram necessarily help to predict whether a good fall in right ventricular pressure will occur after closure of the defect (Cleland *et al.*, 1958).

Nevertheless, in general the presence of left ventricular hypertrophy is likely to be associated with a large left to right shunt, and low pulmonary vascular resistance.

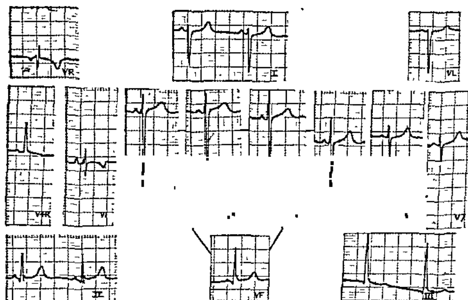


FIG 81 "Eisenmenger" type patent ductus arteriosus with high pulmonary vascular resistance and reversed shunt The deep S waves in right praecordial leads suggest some left ventricular hypertrophy in addition to the great hypertrophy of the right ventricle

Conversely, the presence of pure right hypertrophy has a sinister connotation and suggests that considerable pulmonary vascular disease is present, unless there is pulmonary stenosis. Fig. 80a shows the cardiogram of a boy with a ventricular septal defect, normal pulmonary artery pressure, and pulmonary blood flow of three times the systemic flow. Fig 80b shows the cardiogram of a patient whose right ventricular pressure failed to fall after closure of the defect and who died after operation· there is marked right ventricular hypertrophy

Patent ductus arteriosus. When the ductus is small the cardiogram is normal, or shows modest left ventricular hypertrophy. Any signs of right ventricular enlargement suggest either appreciable pulmonary hypertension or pulmonary stenosis. In cases with reversed flow from birth, there is moderate or severe right ventricular hypertrophy (Fig 81).

In infancy, of course, the cardiogram usually shows right ventricular hypertrophy, unless the ductus is very large, when some evidence of left hypertrophy may be present.

of right ventricular preponderance and five showed right axis deviation In the other cases there were deep negative deflections in leads I and III, with right ventricular hypertrophy.

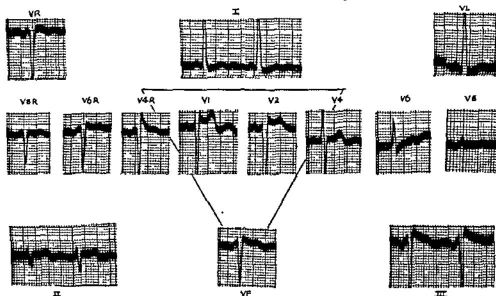


FIG 83(*a*) Tricuspid atresia Note left ventricular hypertrophy (Tall R in VL and deep S in VR) and left axis deviation.

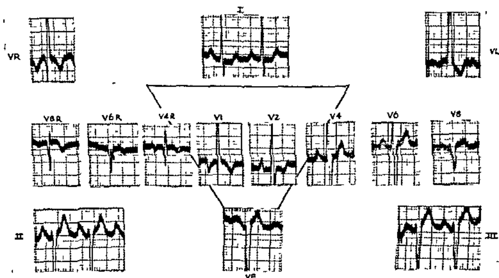
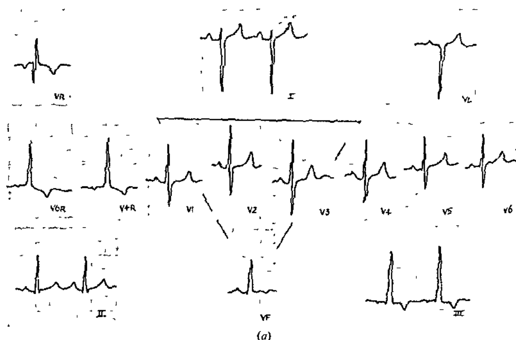


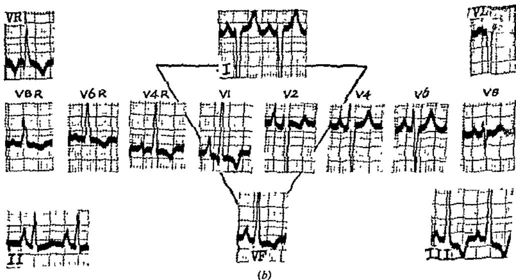
FIG 83 (*b*) Single ventricle with transposition of pulmonary artery and aorta and pulmonary stenosis Note right ventricular hypertrophy and left axis deviation

In transposition with pulmonary stenosis and with single ventricle, there may be right ventricular hypertrophy with left axis deviation (Cleland *et al.*, 1957) (Fig 83b).

ventricular outflow tract, or transposition of the great vessels, with underfilled lungs Campbell *et al.* (1953), reported six cases of single ventricle with pulmonary stenosis and



(*a*)



(*b*)

Fig. 82.

(*a*) Tetralogy of Fallot.
(*b*) Pulmonary stenosis with closed ventricular septum. Note the more severe right ventricular hypertrophy, particularly in V1 and the right atrial P waves.

one with pulmonary atresia. They analysed 78 cases reported in the literature and showed that transposition was present in just over half. Of their seven cases, all showed evidence

2. Acquired Heart Disease

Mitral valve disease. Left atrial enlargement is shown by a broad, notched P wave in many cases and is a useful guide to appreciable left atrial hypertension. Atrial fibrillation occurs in 50 per cent of cases Augmented and pointed right atrial P waves are seen when pulmonary hypertension is extreme, but if present in the absence of any appreciable right ventricular hypertrophy suggest tricuspid stenosis.

The ventricular balance is frequently normal, even in the presence of tight mitral stenosis. Fig 84 shows the valve size at operation and the grade of right ventricular hypertrophy in a series of patients with mitral stenosis. It will be seen that the majority have a normal balance or only grade one hypertrophy. The R/S ratio correlates positively in V4R and negatively in V5 with the height of the right ventricular systolic pressure and the

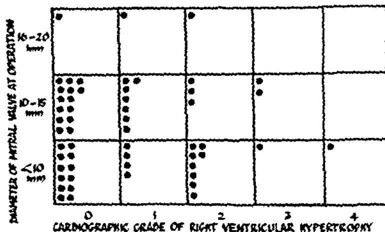


FIG 84 Valve size at operation and cardiographic grade of right ventricular hypertrophy in patients with mitral stenosis Each dot represents one patient

total pulmonary vascular resistance (Fig. 75), while the grade of right ventricular hypertrophy shows a similar trend (Figs. 76 and 77) There is also a positive correlation between the cardiographic degree of right ventricular hypertrophy and the ratio of right to left ventricular thickness (Goodwin and Abdin, 1959).

Thus the cardiogram is of most value in indicating severe pulmonary hypertension, and therefore, usually, extreme mitral stenosis. A grade three cardiogram guarantees a high vascular resistance (TPR around ten units) and, while not excluding mitral incompetence associated with extreme stenosis, rules out the possibility of free insufficiency and makes dominant incompetence unlikely A normal ventricular balance in no way denies tight stenosis. The presence of a left atrial P wave is of great value in diagnosing left atrial hypertension from any cause, but does not of course necessarily indicate mitral valve disease. It is of most help in assisting in the diagnosis of obscure cases of pulmonary arterial hypertension by indicating the presence of left atrial hypertension (Fig 85)

In pure, or dominant mitral incompetence, left ventricular hypertrophy, usually associated with some right, is present, but the left hypertrophy is dominant. Such a pattern

Thus the cardiogram may not be of great diagnostic value, but if other than extreme right axis deviation is present, combined with right ventricular hypertrophy, single ventricle may be suspected. Frank left axis deviation with right ventricular hypertrophy and very high voltage in limb leads may be valuable clues.

In Ebstein's syndrome, complete right bundle branch block, without right ventricular hypertrophy, is present in the majority of cases The diagnosis may be suggested if there

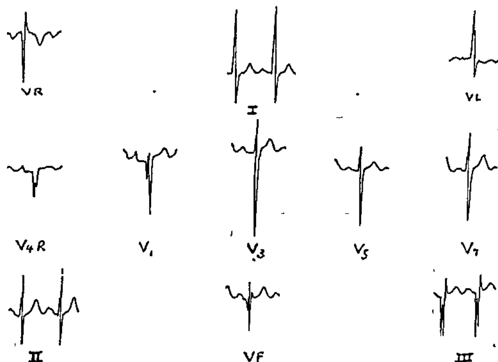


FIG 83 (*c*) Corrected transposition of pulmonary artery and aorta Note left axis deviation, QrS pattern in V1 rS in V5 with long PR interval (0 22/sec) (Leads V3 and V5 ½ sensitivity)

are also right atrial P waves (Goodwin *et al.*, 1953) Left bundle branch block is occasionally seen (Medd *et al.*, 1954).

The Eisenmenger syndrome

As now defined (Wood, 1958) this consists of pulmonary hypertension with reversed central (right to left) shunt. The shunt may be at atrial, ventricular, or pulmonary artery level (Chapter 9)

ventricular
eptal defect
arked right

ventricular dominance. In some other types of Eisenmenger syndrome, especially patent ductus with reversed shunt, the signs of right ventricular dominance are slight, and Q waves may be seen in left praecordial leads (Wood, 1958).

(1951) also noted increase in the S wave in lead V6 in patients with right ventricular hypertrophy due to pneumoconiosis.

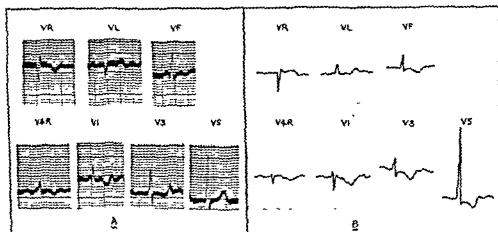


FIG 87 Regression of right ventricular hypertrophy. Before, (*A*), and after, (*B*), mitral valvotomy (ST and T wave changes in (*B*) are the result of digitalis and the cardiotomy)

Left atrial P waves are never seen in cor pulmonale, unless it is complicated by left-sided cardiac disease.

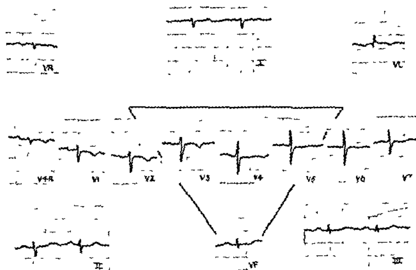


FIG. 88 Right praecordial T inversion and deep S wave in V5 in thrombo-embolic pulmonary hypertension

Mounsey *et al* (1952) compared the right ventricular pressure with the cardiogram in cor pulmonale and showed that the signs of right ventricular hypertrophy increased with the pressure. They considered a persistent rsr′ pattern in lead VI to be *presumptive*, but not certain, evidence of right ventricular hypertrophy, and demonstrated that the

excludes appreciable mitral stenosis unless there is some cause other than mitral incompetence, such as aortic valve disease or systemic hypertension.

Coronary embolism is considered rare, but is perhaps less uncommon in mitral disease than is usually thought. The cardiogram suggests cardiac infarction, usually anterior, and may cause confusion with acute right ventricular enlargement or pulmonary embolism Fig. 86 shows the cardiogram from a patient before and after a coronary embolism. The first tracing shows the normal cardiogram with sinus rhythm. Some months later she



FIG. 85 Left atrial P wave in severe mitral stenosis (lead V5).

suffered an attack of palpitations, followed by crushing substernal pain. The cardiogram at this time showed atrial fibrillation and T wave inversion in leads V2 to 7 and in the standard leads. At mitral valvotomy in November 1958, a myocardial scar was seen in the septal region.

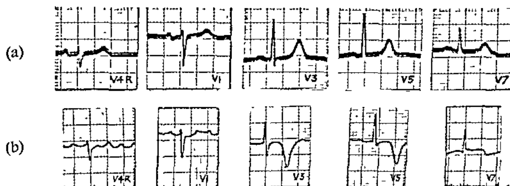


FIG 86 Praecordial leads · (*a*) before, and (*b*) after coronary embolism in mitral stenosis The second tracing shows atrial fibrillation and T wave inversion with ST elevation indicating anterior myocardial necrosis

When, after successful valvotomy, the pulmonary vascular resistance falls, the cardiogram shows a reduction in the degree of right ventricular hypertrophy if this was appreciable before operation, and is thus often a useful guide to improvement (Goodwin *et al.*, 1955) (Fig. 87).

Pulmonary heart disease. In this condition the cardiogram is very variable. Many cases show little or no evidence of right ventricular hypertrophy, even though it is present at autopsy. A greater proportion of cases of pulmonary heart disease than of mitral stenosis show moderate or severe (grade two or three) hypertrophy. Predominantly positive deflections in the ventricular complexes in right praecordial leads are frequently absent, and a dominant R in VR is often present This combination is suggestive of cor pulmonale, especially if right atrial P waves occur, and there is considerable right axis deviation. The deep S in V5 is more common than in mitral stenosis (Goodwin and Abdin, 1959). Thomas

do not usually show low voltage and inverted or flat T waves, although some forms of cardiomyopathy may be an exception.

ACUTE RIGHT VENTRICULAR HYPERTENSION AND ENLARGEMENT

Acute right ventricular embarrassment may occur in pulmonary embolism, in the exacerbations of bronchitis in patients with cor pulmonale, and in acute heart failure in mitral stenosis.

In pulmonary embolism the cardiogram does not show any appreciable change unless the right ventricle is considerably embarrassed. The most characteristic changes occur in the frontal QRS vector, which is rotated to the right, producing right axis deviation, with a characteristic pattern in the standard leads consisting of a prominent S wave in lead I and Q wave in lead III. The ST segment is iso-electric, and the T waves upright in lead I and inverted in lead III. The deep S in I, with iso-electric ST segment and upright T wave has been termed the "step-ladder" pattern. Lead VF is usually normal, but may show an inverted T wave Lead VR sometimes has a dominant R wave Right atrial P waves are not uncommon and reflect right atrial strain.

The praecordial leads reflect the clockwise rotation of the horizontal vector, for there is often a prominent, or deep S wave in V5. T wave inversion may occur from V1 to V5, or more often as far as V3. Wood (1941) pointed out the importance of T wave inversion in lead CR1 in which the T wave is normally upright, and this is a valuable lead to record if pulmonary embolism is suspected A dominant R wave may appear in lead V4R or V1, and partial right bundle branch block is not uncommon. Complete right bundle branch block occasionally occurs as the sole cardiographic sign of pulmonary embolism, and is then transient

The pattern in the limb leads has some features in common with posterior cardiac infarction, but there are important differences The ST segment is never elevated in pulmonary embolism because there is no current of injury, and the Q wave present in lead III is not reflected in lead II, as in posterior infarction Since there is no current of injury there is no reciprocal depression of the ST segment in lead I, in pulmonary embolism. nor does VF show the Q wave of posterior infarction

The tall T waves seen frequently in the praecordial leads in posterior infarction are not present in pulmonary embolism, while the deep S wave in V5 in pulmonary embolism is not seen in posterior infarction (Fig 90)

The rapid resolution of the cardiographic changes and the return to a normal pattern is an important feature of pulmonary embolism, and serial cardiograms at short intervals are of great value. Acute right ventricular stress due to other causes tends to produce a similar picture to pulmonary embolism, but the changes in the limb leads are not usually so characteristic.

The reversibility of the signs of right ventricular enlargement is well shown in patients with chronic cor pulmonale or mitral stenosis, in whom signs of right ventricular hypertrophy may develop and regress in a matter of weeks This is especially true in V4R in which the R wave may become dominant during an attack of heart failure, and decrease to normal size on recovery (Camerini *et al*, 1956).

This suggests that hypertrophy of the ventricular wall is not the major cause of

small secondary "r" wave grew until it dominated the QRS complex, as the right ventricular pressure rose.

Atrial fibrillation is unusual in cor pulmonale without left ventricular disease and should suggest the presence of another lesion (such as ischaemic heart disease) or an alternative cause for right ventricular hypertrophy.

Primary, or lone, pulmonary hypertension. Severe cases show extreme degrees of right ventricular hypertrophy, and often T wave inversion in right praecordial leads, even though the right ventricular systolic pressure does not exceed 100 mm. Hg. There are two possible reasons for this First, the cardiac output may be very low as a result of great obstruction to flow through the pulmonary arteriolar bed, so that the right ventricular

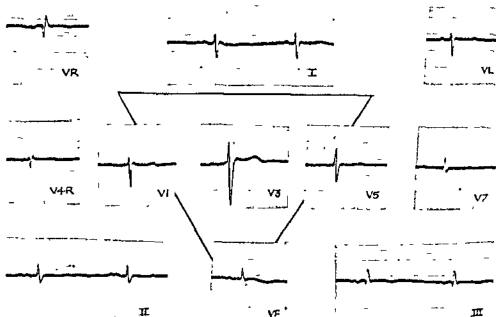


FIG 89 Constrictive pericarditis Note low voltage QRS and T waves and left atrial P waves (Tachycardia is absent in this case)

systolic pressure is not greatly elevated. Second, the increase in load on the right ventricle may be rapidly progressive (perhaps only over a matter of months), and cause rapid enlargement and dilatation of the right ventricle, which is previously unprepared for such an onslaught.

When pulmonary hypertension is due to thrombo-embolism, the cardiogram may show T wave inversion in praecordial leads, as far as V5, with a deep S wave in this lead. This pattern may be helpful in suggesting the diagnosis (Fig. 88). But cases of pulmonary thrombo-embolism involving the major branches of the pulmonary arteries often have dominant R waves in right praecordial leads in addition (Ball *et al*, 1956)

Constrictive pericarditis. The salient features are low voltage, tachycardia (atrial fibrillation in 30 per cent), and flat or inverted T waves. Signs suggesting some right ventricular hypertrophy may be seen. Left atrial P waves are not uncommonly associated and are an important pointer to the diagnosis, for other cases of left atrial hypertension

However, other factors may also be important, such as the duration of the hypertrophy, myocardial disease, and enlargement of the left ventricle (Goodwin and Abdin, 1959). In the congenital group, the pathological right ventricular hypertrophy is added to the physiological, *so that often the left ventricle is never dominant. By contrast, in acquired* hypertrophy, the left ventricle is dominant for many years before the right ventricle enlarges, so that hypertrophy has to be considerable before the normal left ventricular dominance is overcome.

In acquired cases, however, rapid increases in right ventricular work may produce a more severe cardiographic change than in cases with gradual increase in right ventricular load. *This may be due to dilatation and failure of the right ventricle.*

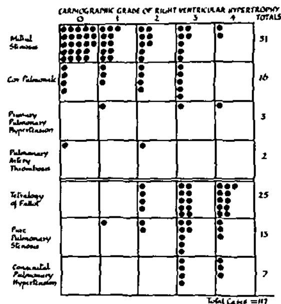


FIG 91. Grades of right ventricular hypertrophy in congenital and acquired heart disease Each dot represents one case

The contribution of myocardial disease is difficult to assess, but conditions such as coronary embolism may modify the signs of right ventricular hypertrophy, while ischaemic heart disease or other lesions may enlarge the left ventricle and thus diminish the signs of right ventricular enlargement.

Undoubtedly, one of the main factors in reducing the signs of right ventricular hypertrophy in acquired disease is associated left ventricular hypertrophy. But misleadingly unimpressive signs of right hypertrophy may occur with a high pulmonary resistance in the absence of left ventricular enlargement, especially in mitral stenosis (Goodwin and Abdin, 1959).

COMBINED VENTRICULAR HYPERTROPHY

Signs of enlargement of both ventricles are found in only about 30 per cent of cases (Pagnoni and Goodwin, 1952). The remaining 70 per cent show either a normal balance, or pure right or left hypertrophy. The signs of combined hypertrophy are as follows:

dominant R waves in right praecordial leads. It seems much more probable that both hypertrophy and dilatation, singly or in combination, rotate the horizontal QRS vector to the right and anteriorly, so that tall R waves appear in right praecordial leads and deep S waves in left praecordial leads. The fact that lead V4R, which is actually further from the right ventricle than V1, shows signs of right ventricular hypertrophy earlier than V1, harmonizes with this view (Camerini *et al.*, 1956). It must be remembered that it is the balance of forces acting on both ventricles which determines the form of the QRS complex. This is illustrated by a patient with mitral stenosis, in whom the R wave in V4R doubled in voltage after the development of right bundle branch block, and reverted to its previous voltage on resolution of the block. The branch block occurred during cardiac catheterization and could not be ascribed to any temporary acute right ventricular dilatation. It is suggested that the presence of the block so altered the balance of forces that

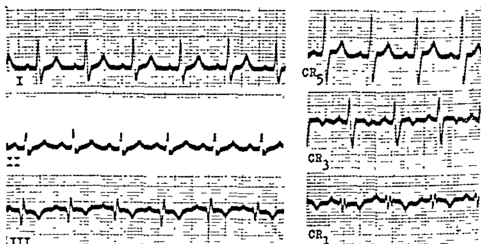


FIG 90 Pulmonary embolism Note rsr′ pattern in CR1 and characteristic changes in standard leads

stronger positive vector forces were directed to V4R. Camerini *et al.*, (1956) have suggested that the alteration of the vector loop in the horizontal plane is due to a combination of factors including alteration of the relative positions of the ventricles, the relative magnitude of their electrical forces, and the direction of spread of the impulse.

In view of the variability of the signs of right ventricular hypertrophy, it is important (especially in acquired heart disease) to base deduction of the degree of chronic right ventricular hypertrophy only upon a cardiogram recorded when the clinical status of the patent is optimal.

RIGHT VENTRICULAR HYPERTROPHY IN ACQUIRED AND CONGENITAL DISEASE

In general, the cardiographic signs of right ventricular hypertrophy are much more marked in congenital than acquired heart disease (Fig 91). This is largely due to the higher right ventricular pressures and greater right ventricular muscle thickness in the former.

VENTRICULAR HYPERTROPHY AND CARDIAC INFARCTION

When one or both ventricles are enlarged, the changes in the chest leads may mask anterior infarction and old anterior infarcts may present cardiographically merely as an rS pattern in V5 (Goodwin, 1958). Rotation of the horizontal QRS vector loop to the right by right ventricular hypertrophy may abolish the antero-lateral negative vector forces of infarction and replace the Q wave by a small r wave in V5. Another reason for the rS pattern in V5 in infarction is the growth of the r wave with healing (Fig. 93)

Whatever the cause, ventricular hypertrophy may mask anterior infarction effectively and thus be very misleading. Concealed infarction is unusual when the heart is strongly vertical or when right atrial P waves are present, and these points provide useful guidance in interpretation.

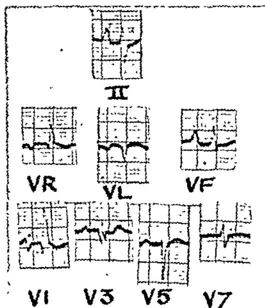


FIG. [illegible]

Conversely, pure right ventricular hypertrophy may closely simulate anterior infarction with q waves in right praecordial leads, presumably due to bizarre rotation of the horizontal vector loop (Fig 94).

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BUR [illegible] e Spatial Vector Cardiogram in Proved Congenital

1. Signs of left hypertrophy with a dominant S wave in V5, and/or a vertical position of the heart (Fig. 92).
2. Signs of left hypertrophy with a dominant R in VR.
3. Signs of right hypertrophy with deep S waves (dominating the R waves) in right praecordial leads, dominant S wave in V5, and horizontal position of the heart.

(Pagnoni and Goodwin, 1952; Goodwin, 1958).

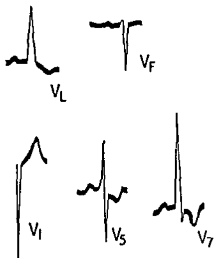


FIG. 92. [illegible] of [illegible] wa[illegible] thic[illegible] car[illegible] *Heart J.* Reproduced by courtesy of the Editor, *British Heart Journal*)

The last combination, in which dominant S waves are present in both right and left praecordial leads, with or without a dominant R in VR, may of course be produced by right ventricular hypertrophy alone, but is always suggestive of additional left ventricular enlargement. In such cases the left ventricular hypertrophy has probably neutralized the R waves in right praecordial leads.

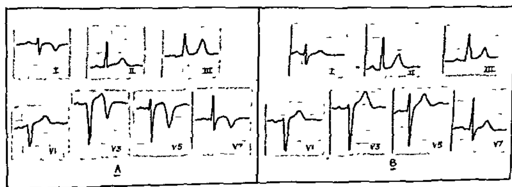


FIG. 93. Healing of cardiac infarction showing in (*B*) rS pattern developing from QS and qrS patterns in V3 and V5 (*A*). T wave inversion has disappeared

CHAPTER 8

MITRAL VALVE AND LEFT ATRIAL DISEASE

BY JOHN GOODWIN

MITRAL STENOSIS

Haemodynamics. In all forms of mitral valve disease except free incompetence, obstruction to left ventricular inflow is present and has pronounced effects upon the lesser circulation As a result of the obstruction, the left atrial pressure rises, and pulmonary venous hypertension ensues. The cardiac output is initially normal and this helps to maintain the high left atrial pressure As has been mentioned in Chapter 4, the pulmonary arterial pressure rises passively in order to maintain the normal gradient across the capillary bed. Following this, changes develop in the pulmonary veins and arterioles, the latter causing a further increment in pulmonary artery pressure. Thus in severe mitral stenosis three forms of pulmonary hypertension are present: venous hypertension; "passive", and "active" arterial hypertension

When mitral stenosis is of slight or moderate degree, the valve orifice is quite large enough (around 2·5 sq cm) to allow an adequate blood flow without a rise in left atrial and pulmonary vascular pressures. But when the valve is smaller, the left atrial pressure rises proportionately to the severity of the stenosis, and may reach a level of 20–25 mm Hg above the sternal angle at rest An adequate output can only be obtained at the expense of such high left atrial and pulmonary venous pressures At this stage of the disease, acute pulmonary oedema may occur if the pulmonary venous pressure rises suddenly to a yet higher level. The colloid osmotic pressure of the plasma is then exceeded, and fluid transudes from the capillaries into the alveoli. Exercise, excitement, fever, pregnancy, may all cause acute pulmonary oedema in mitral stenosis. The common factor is probably tachycardia, which reduces the time available for ventricular filling, and elevates further the left atrial pressure. In pregnancy, the increased blood volume and cardiac output are of major importance in predisposing to pulmonary oedema

As the pulmonary venous pressure rises, the pulmonary artery pressure follows in a linear fashion as long as the left atrial pressure is below approximately 20–25 mm Hg. When this figure is exceeded there is a sharp rise in arterial pressure, quite beyond that which would be due to a mere passive increase (Holling, 1952; Lewis *et al.*, 1952). This is "active" arterial hypertension, and is due to reduction in the lumen of the arterioles, with consequent increase in arteriolar resistance The discrepant increase in arterial pressure with high levels of pulmonary capillary "wedge" (indirect left atrial) pressure is shown in Fig 95 in a series of patients with mitral valve disease. The problems of the increased arteriolar resistance in mitral stenosis will now be discussed.

"Active pulmonary hypertension." The increase in arteriolar resistance which is the basis of this form of pulmonary hypertension might be due either to vasoconstriction, or

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pulmonary artery pressure and mixed venous oxygen saturation. Thus undue desaturation of mixed venous blood reaching the pulmonary arterioles might possibly bring about vasoconstriction.

Davies *et al.* (1954), Balchum *et al.* (1957) and Goodwin *et al.* (1958) claimed that pulmonary vasodilatation could be produced in mitral stenosis with hexamethonium, suggesting release of neurogenically maintained vasoconstriction. Their results have been discussed and illustrated in Chapter 4. The demonstration of a direct relationship between the initial level of the pulmonary artery pressure and the extent of the fall induced by hexamethonium is also in harmony with vasoconstriction, and the same relationship was found by Braun *et al.* (1957) with Priscoline.

The most striking evidence of vasoconstriction has been obtained by Wood (1958) using acetylcholine. He found that this drug produced a fall in pulmonary vascular resistance and a rise in left atrial pressure in fourteen of sixteen patients with mitral stenosis. But the findings of Söderholm and Werko (1959) of a reduction of arterial oxygen saturation after acetylcholine suggest that other factors may be implicated.

There is therefore strong evidence for pulmonary arterial vasoconstriction in mitral disease, and consideration must now be given to pathological and radiological studies.

Larrabee *et al* (1949) described intimal fibrosis and necrotizing changes in the arterioles and thought that these might be the cause of the increase in resistance There is no doubt that such changes may be present, for Bayliss *et al.* (1950) showed them in two of their patients, and Harrison reported local areas of atheromatous intimal thickening in thirteen of thirty cases (Doyle *et al*, 1957). But these changes were all of a localized nature and involved too few arteries to influence the resistance significantly. They are almost certainly due to the effects of a high pressure on the pulmonary vascular tree and may be secondary to thrombo-embolism.

A more generalized abnormality of the pulmonary vessels would be required to elevate resistance and this was found in angiographic studies (Goodwin *et al.*, 1952; Davies *et al.*, 1953 and Doyle *et al*, 1957) These findings have been fully described in Chapter 5. To recapitulate briefly, reduction in the lumen of the muscular arteries to the lower lobes was constantly found in patients with moderate or severe pulmonary hypertension The upper lobe arteries were always normal, or even enlarged Post-mortem angiography by Professor C V. Harrison confirms these findings (Chapter 6), the changes being if anything more marked. The narrowing was smooth and regular, and histological studies showed medial hypertrophy in the small muscular arteries, which was always greater in the lower than in the upper zones. The intima was normal, except in the few scattered areas already mentioned in Chapter 6. Post-mortem perfusion with fluoride increased the calibre of the arteries, indicating release of constriction which had persisted after death.

Dollery and West (1960) working at the Postgraduate Medical School have obtained further evidence of reduced blood flow to the lower zones in mitral stenosis from studies with carbon dioxide labelled with radioactive oxygen ($C^{15}O_2$) When the gases are inhaled there is a more rapid clearance from the upper than the lower zones, indicating greater flow to the former. Similar studies in normal subjects have shown exactly the reverse (Fig. 96).

These results are in harmony with the other evidence for pulmonary vasoconstriction in mitral disease.

to organic occlusive changes in the arterioles, or to both. The available evidence strongly indicates that vasoconstriction is the prime cause. In 1948, Hickam and Cargill showed that exercise produced a marked increase in pulmonary artery pressure but a much less impressive rise in output, in contrast to the normal response of a rise in output but little or no rise in pressure. In the normal subject the pulmonary vascular resistance falls on effort, but in the mitral patient it rises. The rise in resistance on effort cannot be due to an increase in mitral obstruction and must be due to the increase in left atrial pressure already mentioned, and to narrowing of the arterioles. A fixed obstruction in the arteriolar bed due to organic narrowing of the vessels would also tend to produce a rise in pressure with little or no rise in output, but Bayliss *et al.* (1950) confirmed the observations of Hickam

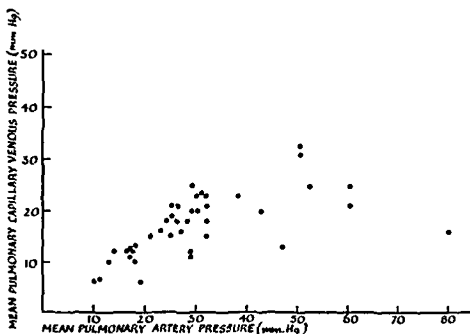


FIG 95 Mean pulmonary arterial and pulmonary capillary venous (wedge) pressures in mitral stenosis. Each dot represents one patient

and Cargill, and showed that the pulmonary arterial pressure can increase with heart failure and decrease with recovery, suggesting a reversible process due to vasoconstriction.

Further evidence for vasoconstriction comes from acute studies with drugs and other agents.

McGregor *et al.* (1953) showed that inhalation of pure oxygen reduced the pulmonary resistance in ten of thirteen patients with mitral stenosis, and suggested that hypoxia might be a factor in maintaining pulmonary hypertension. Yu *et al.* (1956) reported the results of breathing a low concentration of oxygen in 24 patients with mitral stenosis. The pulmonary vascular resistance rose and subsequently fell during recovery, again suggesting stimulation of vasoconstriction by hypoxia and subsequent release by increase in oxygen tension. Holling and Venner (1956) showed that there was an inverse relationship between

pulmonary artery pressure and mixed venous oxygen saturation. Thus undue desaturation of mixed venous blood reaching the pulmonary arterioles might possibly bring about vasoconstriction.

Davies *et al* (1954), Balchum *et al.* (1957) and Goodwin *et al.* (1958) claimed that pulmonary vasodilatation could be produced in mitral stenosis with hexamethonium, suggesting release of neurogenically maintained vasoconstriction. Their results have been discussed and illustrated in Chapter 4. The demonstration of a direct relationship between the initial level of the pulmonary artery pressure and the extent of the fall induced by hexamethonium is also in harmony with vasoconstriction, and the same relationship was found by Braun *et al.* (1957) with Priscoline.

The most striking evidence of vasoconstriction has been obtained by Wood (1958) using acetylcholine. He found that this drug produced a fall in pulmonary vascular resistance and a rise in left atrial pressure in fourteen of sixteen patients with mitral stenosis. But the findings of Söderholm and Werkö (1959) of a reduction of arterial oxygen saturation after acetylcholine suggest that other factors may be implicated.

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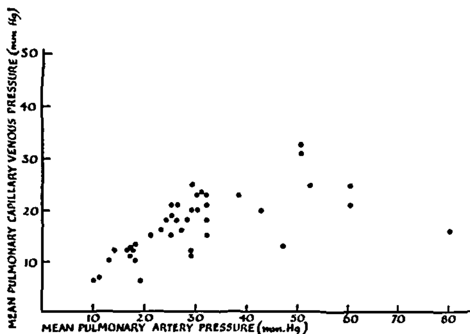


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stimulation [illegible]
tension. H[illegible]

lobe veins, and by the angiographic demonstration of venous as well as arterial constriction, confined to the lower lobes (Simon, 1958; Goodwin, 1958) (Chapters 5 and 6) Fig. 97 shows this concept diagrammatically.

The exact fashion in which the arteries respond to the stimulus of venous hypertension is not known, but a reflex pathway may be involved Wade *et al* (1956) have postulated a "local" reflex, uninfluenced by the autonomic nervous system, while Dawes (1959) believes that both pressure and volume receptors are present in the left atrium, although it is not certain whether these have any direct association with the pulmonary circulation Eliakim *et al.* (1958) claimed that receptors are present at the junction of left atrium and pulmonary veins, but doubt has been cast upon this suggestion (Semler *et al.*, 1959).

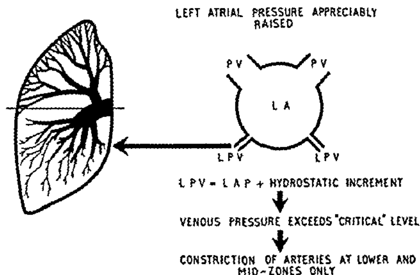


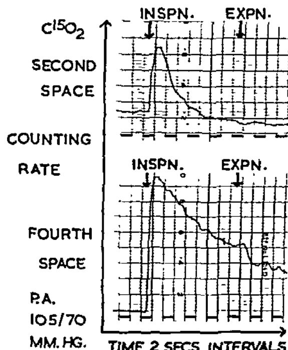
FIG 97 Concept of pulmonary venous and arterial changes in mitral stenosis
L P V. = pulmonary veins to lower zones
L A P = left atrial pressure
P V = pulmonary veins to upper zones

Our own work with hexamethonium suggests that the autonomic nervous system is probably involved in the reaction, but the exact pathway is unknown (Chapter 4). Moreover, other factors are probably implicated Local hypoxia may stimulate venous and arterial constriction, either by a direct action upon the vessels or via a neurogenic mechanism. The stiffness and inelasticity of the lungs demonstrated by Marshall *et al* (1954) may predispose to local hypoxia, but it must be noted that arterial desaturation is not a feature of mitral stenosis, although the mixed venous saturation is often unduly low, as a result of the low cardiac output and increased oxygen extraction by the tissues

While there is abundant evidence that in mitral valve disease the pulmonary vascular resistance rises with the left atrial and pulmonary venous pressure, work in cats has shown that increasing left atrial pressure to 15 cm. saline decreased pulmonary vascular resistance and increased pulmonary blood volume, suggesting that the increase in left atrial pressure

The cause of the vasoconstriction, the factors which precipitate it, and the reasons for the localization of the arterial changes, will now be discussed.

The consistent fashion in which arteriolar constriction follows high levels of left atrial pressure suggests a connection between the two. Lasser and Loewe (1954), working with experimental mitral stenosis in dogs, showed that the pulmonary artery and left atrial pressures rose in linear fashion, until the latter reached 30–40 mm. Hg, after which the increase in the arterial pressure was proportionately greater than in the venous. This



finding agrees with the catheterization studies in man already quoted and suggests that left atrial hypertension precipitates pulmonary artery and arteriolar constriction, and is supported by the contention of Wade *et al.* (1956) that when hexamethonium lowers the pulmonary artery pressure in mitral stenosis, there is always a preceding fall in left atrial pressure.

We (Doyle *et al*, 1957), have attempted to explain the localization of arterial changes to the lower lobes of the lungs by postulating a critical level of atrial pressure which, when augmented by the hydrostatic pressure imposed by gravity, stimulates arterial constriction. This hypothesis is supported by the finding of muscular hypertrophy in the lower

First, an increase in the thickness of the capillary wall, alveolar basement membrane, and interstitial tissue which resists the passage of fluid through them into the alveoli (Hayward, 1955). Fluid, however, does pass into the interstitial tissue, and is partially removed by the lympathatics which then become engorged. Second, Gilroy *et al.* (1952) pointed out that the true bronchial veins drain into the pulmonary veins and suggested that the raised pulmonary venous pressure would thus be transferred to the bronchial veins, leading to interstitial but not intra-alveolar, pulmonary oedema. They drew attention to the fact that the pleuro-hilar (extra-pulmonary) bronchial veins (which drain into the azygos, hemiazygos, and intercostal veins) communicated freely with the pulmonary veins, and were dilated and varicose in mitral stenosis. This suggested a safety valve for relieving extreme pulmonary venous hypertension and preventing acute pulmonary oedema.

Thirdly, in some cases of mitral stenosis the pulmonary venous pressure is surprisingly low and the pulmonary resistance unimpressive as a result of a very low cardiac output. The low output is associated with considerable cardiac enlargement and a myocardial fault has been postulated.

Fourthly, Wood suggested that the pulmonary arteriolar constriction already described exerts a protective effort by imposing a barrier to the development of a very high pulmonary venous pressure and pulmonary oedema This may be so when the arteriolar resistance is extreme as a result of a most intense degree of arteriolar constriction. Such patients have the symptoms principally of fatigue, as a result of a low cardiac output, and may readily develop right ventricular failure (MacKinnon *et al.*, 1956). The very high arteriolar resistance may damp left atrial flow to such an extent that the classical murmur may be minimal, the radiological signs of pulmonary venous hypertension only slight and the left atrium misleadingly small. But such cases are the exception rather than the rule, and pulmonary oedema can certainly occur in subjects with evidence of arteriolar vasoconstriction However, the narrowing in the basal vessels diverts acute massive oedema to the central part of the lung, and in this sense might be regarded as locally protective. Furthermore, if arteriolar constriction were of such importance in restricting left atrial pressure, patients might be expected to develop pulmonary oedema after receiving drugs such as acetylcholine which produces arteriolar vasodilation, which is not the case. Holling and Venner (1956) in an intensive study of the circulatory changes in mitral stenosis, inclined to the view that if the increased arteriolar resistance "protects" the capillaries at all, this protection fails easily, since the pulmonary capillary pressure always rises appreciably on exercise. But they noted no evidence of increased fluid in the lungs after exercise in their patients. The capillaries are certainly subjected to an increased pressure on exercise, and the fact that this does not invariably cause pulmonary oedema is due to factors other than a restrictive effect of the increased pulmonary arteriolar resistance.

In the author's view arteriolar constriction is the least important influence which protects against pulmonary oedema, the most important being the chronic changes in the walls of capillaries and alveoli resulting from long-standing pulmonary venous hypertension.

As would be expected, pulmonary oedema usually develops most readily when the valve is critically stenosed, but this is not always the case. It may occur in patients with larger valves in response to an overactive right ventricle, extreme tachycardia, and salt and fluid retention, as in pregnancy.

passively distended the pulmonary vessels, thus increasing flow and reducing resistance (Carlill and Duke, 1956). The circumstances of these observations are very different from those obtained in mitral disease, for in the latter there is chronic left atrial hypertension, pulmonary venous constriction and an abnormal pulmonary vascular bed. However, it is worth considering the possibility that pulmonary venoconstriction may be a more important factor than left atrial hypertension in causing arteriolar constriction, which might not then occur if an acute increase in left atrial pressure was unaccompanied by venoconstriction.

Pulmonary Oedema in Mitral Stenosis

As has already been mentioned, patients with mitral stenosis are at risk from pulmonary oedema, living as many of them do, with a left atrial pressure on the threshold of the colloid osomotic pressure of the plasma Tachycardia produces even greater left atrial hypertension.

The characteristic distribution of acute pulmonary oedema is in the central core of the lung, spreading bilaterally from the hilum like a fan. It spares the extreme apices and the bases. Since acute oedema represents a massive form of pulmonary transudation it might be expected to involve principally the lower lobes. In the lower lobes the veins are narrowed, and although the pressure is high, changes have occurred in the alveolar walls which tend to resist transudation. In the mid-zones, however, there is less hypertrophy of the medial coats of veins, and transudation can therefore occur the more readily

It has been suggested that acute massive oedema is diverted from the bases of the lungs to the mid-zones because of the locally protective influence of the venous and arterial constriction at the bases (Doyle *et al*, 1957) The importance of gravity in determining the site of pulmonary oedema is probably appreciable, and is shown by a personal case, a woman with mitral stenosis, who developed unilateral pulmonary oedema after sleeping on her right side. The radiograph showed massive oedema involving principally the right lung, and clearing rapidly with treatment (Chapter 5, Figs 38a and b)

The persistently raised left atrial and pulmonary venous pressures in mitral stenosis cause progressive transudation from the capillaries This transudation is most marked at the bases and produces the characteristic radiological features described in Chapter 5. It may be regarded as a low grade form of chronic pulmonary oedema in contrast to the acute massive type already mentioned.

There are thus two types of pulmonary oedema in mitral stenosis; chronic, occurring at the bases; and acute, diverted to the central core of the lungs by the narrowing of the basal vessels It is of interest in this connection to quote Drinker's (1954) view that although increased capillary pressure does increase the tissue fluid in the lungs, this fluid rapidly enters the lymphatics, and conventional pulmonary oedema is not seen until lymph stasis occurs. "Something more than increased capillary pressure is necessary to cause oedema" (Drinker, 1954)

It is perhaps surprising that all patients with serious mitral disease do not develop massive oedema, for their pulmonary venous pressure is often at or near the colloid osmotic pressure of the plasma, and certainly rises above it during effort. There must therefore be some protective or compensatory mechanism to prevent pulmonary oedema occurring frequently. According to Wood (1956) there are four such possible protective mechanisms.

The Lungs in Mitral Stenosis

Haemosiderosis, when severe, is associated with leathery, stiff lungs, which inflate with difficulty and may be commented upon by the surgeon at valvotomy. It does not correlate with any other particular finding, except haemoptysis, which is almost invariable. Attempts have been made to correlate the histological changes in the lungs with the clinical severity of mitral stenosis and the results of mitral valvotomy, but without much success. Goyette *et al.* (1954) studied material from lingular biopsies obtained at thoracotomy for mitral stenosis. They noted capillary dilatation, thickening of the capillary basement membrane, increase in interstitial tissue, and pericapillary oedema. The pulmonary vessels showed intimal thickening, medial hypertrophy and scarring, these changes being more common in older patients with severe disease and in those with radiological evidence of haemosiderosis, and increased pulmonary vascular resistance. It was not possible to predict which patients would do well after valvotomy from the microscopic changes, but usually the results were less good in the patients with the most marked changes.

It is, of course, questionable whether the lingula is representative of the whole lung, and this may well not be so in view of the different distribution of vascular changes noted by Doyle *et al.* (1957) (Chapters 5 and 6).

The Influence of Valve Size upon the Pulmonary Circulation

The degree of pulmonary arterial hypertension varies roughly in proportion with the severity of the stenosis, and although a critically small valve may on occasions be associated with only moderate hypertension, severe hypertension guarantees a very narrow valve, unless appreciable incompetence is present.

The left atrial pressure, measured indirectly by wedging the cardiac catheter in a small branch of the pulmonary artery (pulmonary capillary venous pressure) is always elevated, except in mild cases, and is the best evidence of the degree of mitral obstruction Using a reference point 5 cm. blow the sternal angle, the maximum normal mean left atrial pressure is around 10 mm Hg. In severe cases the pressure may reach 20–30 mm Hg, and rise still further on exercise. The pulmonary arteriolar resistance may be derived from the equation:

$$\frac{\text{Mean pulmonary arterial pressure } \textit{minus} \text{ Mean pulmonary capillary venous pressure}}{\text{Cardiac output (litres/min.)}}$$

The resistance is normally about one unit, but in critical mitral stenosis is often about four to five units, being around ten units in a minority of severe cases. The following examples may be quoted.

(1) $$R = \frac{MPAP(36) - MPCVP(20)}{CO \text{ (4 litres/min.)}} = 4 \text{ units}$$

where R = pulmonary arteriolar resistance
$MPAP$ = mean pulmonary arterial pressure (mm. Hg)
$MPCVP$ = mean pulmonary capillary venous pressure (mm. Hg)
CO = cardiac output (l./min.)

(2) $$R = \frac{60 - 24}{3} = 12 \text{ units}$$

Pulmonary Function in Mitral Stenosis

The chronic vascular abnormalities in the lungs produce impairment of lung function. Marshall *et al* (1954) studied respiratory function in patients with mitral stenosis at rest and on exercise. They found that the work of breathing was increased slightly at rest and that on exercise the work required to ventilate the lungs was two or three times greater than in normal subjects This increased work on effort was due mainly to an increase in elastic resistance, which they considered to be the result of rigid congested lungs. The dyspnoea of which patients complain is probably the result of the increased work of breathing, and upon the increase in respiratory rate which follows the increase in elastic resistance of the lungs.

This increase in lung stiffness is presumably due to the effects of chronic interstitial oedema, increase in thickness of alveolar and capillary walls, and possibly some intra-alveolar oedema It is not apparently due to an elevated pulmonary blood volume, for Kopelman and Lee (1951), found that this was only very slightly increased.

Garbagni *et al.* (1958) found an increased residual lung volume in mitral disease which they attributed to reduced pulmonary elasticity, due to the factors mentioned above The hypertensive pulmonary arterial tree might provide a rigid framework for the lung, for McIlroy and Apthorp (1958) noted that patients with pulmonary hypertension from any cause tended to show a variable reduction in lung compliance, diffusing capacity, and ventilation equivalent, with a slight rise in inspiratory resistance. They considered that there was no direct relationship between pulmonary hypertension and impairment of respiratory function, the latter being usually caused by other factors which accompanied pulmonary hypertension, such as interstitial transudation, disease of the parenchyma of the lung, and occlusive changes in the pulmonary vascular bed Increase in airway resistance may also impair respiratory function in mitral stenosis, for wheezing, with tenacious, often infected, sputum is common, and may be accompanied by swelling of the bronchial mucosa.

West *et al.* (1953) studied respiratory function in relation to dyspnoea in 21 patients with mitral disease. Three of these had additional pulmonary disease, while the remaining 18 had cardiac disease only and were not in heart failure. In the second group, there was no abnormality in lung volume, maximum breathing capacity was slightly reduced, and pulmonary ventilation slightly increased. This hyperventilation was considered to be physiological in type since the arterial P_{CO_2} was often low at rest and after exercise. The cause of hyperventilation was not apparent, but it might have been due to increased activity of receptors sensitive to changes in tension in the pulmonary vessels or in the lung. Oxygen consumption was normal at rest, but less than normal on exercise in the minority of the eighteen patients. By contrast the three patients with additional pulmonary disease [illegible]

muscles due to low cardiac output might also increase the effort of breathing and cause dyspnoea. This view is supported by the frequent complaint of fatigue and lassitude in patients with severe mitral stenosis

The cardiac output can afford some guide to the severity of stenosis, as Gorlin and Gorlin's figures show. In the absence of myocardial disease, a low fixed output indicates severe stenosis and considerable pulmonary vascular disorder. The low output is largely the result of a low mixed venous oxygen saturation due to high tissue extraction of oxygen. Holling and Venner (1956) showed that in patients with the greatest disability, the greatest changes occurred in mixed venous blood oxygen saturation and pulmonary artery pressure,

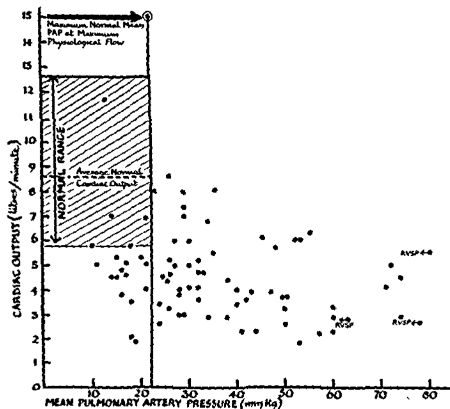


FIG [illegible]

there being an inverse relationship between the two. Since a high pulmonary artery [illegible]

Fig. 98, in which the mean pulmonary arterial pressure is plotted against the cardiac output in seventy-seven patients with mitral stenosis. In the majority the output is low and tends to vary inversely with the pressure, as would be expected. The restrictive effect of pulmonary hypertension upon output is well illustrated, while two cases are of especial

The second example illustrates the increase in pressure gradient between arterioles and capillaries which results from extreme vasoconstriction of the arterioles.

Gorlin and Gorlin (1951) devised a formula for predicting the valve size in mitral stenosis from haemodynamic data.

$$MVA = \frac{MVF}{31 \sqrt{\text{"}PC\text{"} - 5}}$$

where MVA = mitral valve area in cm^2

MVF = mitral valve flow c c per diastolic sec. = $\dfrac{\text{Cardiac output (c.c./min.)}}{\text{Diastolic filling period (sec. per min.)}}$

"PC" = pulmonary capillary mean pressure mm. Hg

5 = assumed left ventricular diastolic pressure mm. Hg

31 = empirical constant

It will be seen that two assumptions are necessary in this formula, but despite this it gives a good rough approximation to valve size as measured by the surgeon at thoracotomy. Lewis *et al.* (1952) showed that with a normal valve area of 4 0 cm^2 a normal valve flow of 150 ml per diastolic sec could be accomplished with a low (normal) head of pressure in the left atrium. As the valve area became progressively smaller the left atrial pressure rose, and the flow diminished, so that at a valve area of 1 cm^2 the left atrial pressure necessary to maintain a normal flow must be around 25 mm Hg. They found that a positive correlation between the cardiac index (cardiac output in litres/min per sq m of body surface) and the mitral valve area, the former being 2 5 or less when the valve area was less than 1 cm^2 They found an inverse correlation between pulmonary arteriolar resistance and valve area, showing that the smaller the valve the higher the resistance. The same relationship held for pulmonary arteriolar resistance and cardiac index. Therefore, it is clear that the smaller the valve the higher the venous pressure and the arteriolar resistance, and the lower the output. Both obstruction at the mitral valve and the arteriolar vasoconstriction contribute to restriction of cardiac output. A valve area of around 1 0 cm^2 appears to be highly critical on the production of severe haemodynamic disturbance

It is not necessary routinely to employ the Gorlin formula to predict valve size from haemodynamic data, for substantial elevations of pulmonary artery and pulmonary capillary pressure guarantee a small valve orifice, providing important incompetence is not associated. Thus a mean pulmonary artery pressure of around 40 mm Hg, mean venous pressure of about 20, and resistance of four to six units indicates a valve area of 1 or less than 1 cm^2, while a mean pulmonary artery pressure of 10–15 mm. Hg, mean venous pressure of 10–15 mm Hg and normal resistance indicates a larger valve, probably 2–3 cm^2. From the aspect of treatment, patients with valve areas of 1·5 cm^2 or less, require surgical relief, those with valves 1 8–2 cm^2 are in the borderline group and those with valves larger than 2 cm^2 are not in need of valvotomy The same figures can be related to valve diameter as measured by the surgeon at operation. Exceptions may occasionally be made in the last group, when valvotomy may be indicated to prevent recurrent systemic emboli. Such emboli usually occur with tight stenosis, but occasionally complicate less severe obstruction, and may be the only disability.

and left atrium. All three abnormalities are the direct result of obstruction to left ventricular inflow. The slow "y" descent is the result of delay in ventricular filling, while the pressure gradient reflects the efforts of the left atrium to force blood through the narrowed valve As would be expected, the higher the left atrial pressure and the mitral gradient, the tighter the stenosis. The rate of "y" descent is of course inversely related to the severity of the stenosis Fig 99 shows the pulmonary capillary venous pulse, and Fig. 100 the mitral valve gradient, in mitral stenosis

When atrial fibrillation is present the "a" wave disappears, and the "v" wave is often large, Fig 101a.

The form of the left atrial pulse may give information regarding the presence or degree of mitral regurgitation, though simple inspection may be very fallacious. The presence of a large "v" wave is common to both stenosis and incompetence. Wynn *et al.* (1952)

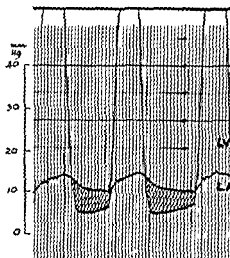


FIG 100 Simultaneous left atrial and left ventricular pressures in mitral stenosis Diastolic mitral valve gradient (shaded) 5 mm Hg
LA = left atrium = v 14 mm Hg
y 10 mm Hg
LV = left ventricle = 75/5 mm Hg
(Courtesy of Dr A Hollman)

concluded that the presence of associated mitral incompetence did not significantly alter the form of the stenotic pulse, and noted that with atrial fibrillation the atrial pressure rose abruptly with the onset of ventricular contraction, and that this was not necessarily due to a regurgitant jet of blood through the valve

The diastolic component of the left atrial pulse is more significant however In 1955 Owen and Wood introduced a formula for relating the rate of descent of the "y" slope to the height of the "v" wave, the Ry/v Ratio (Ry = rate of "y" descent) Study of a number of left atrial pressure pulses showed that the height of the "v" wave was proportional to the rate of "y" descent under all circumstances The ratio is obtained by measuring the rate of "y" descent in mm. Hg per sec, and dividing this by the height of "v". In severe mitral stenosis the ratio is between 0·6 and one In the absence of any significant obstruction as in pure mitral incompetence, left ventricular failure, or constrictive pericarditis, the ratio lies between two and six Borderline cases with some stenosis and marked incompetence, or with mild stenosis only, have ratios in the region of 1 6. Appreciable, but not extreme, stenosis has a ratio between 1 and 1 5 The ratio does not necessarily detect the presence of mitral incompetence, but merely indicates the presence

interest since they show a very low output (about two litres per minute) with a normal pulmonary artery pressure. In these patients severe myocardial damage may be postulated, although it must be remembered that if the flow is extremely low, the pressure will be damped also, so that the calculated resistance may not be raised. In cases with a low output and low pressures the suspicion of myocardial damage may be difficult to substantiate, but would be strengthened by the presence of undue cardiac enlargement or certain cardiographic changes (Chapter 7).

The Pulmonary Capillary Venous and Left Atrial Pressure Pulses

If the cardiac catheter is firmly wedged in a small peripheral branch of the pulmonary artery, a pressure pulse is obtained which reflects that of the left atrium (Hellems *et al.*, 1948). The pulse is of venous type, and is identical with that of the left atrium, as shown by Epps and Adler (1953) who compared immediately consecutive pulmonary "wedged"

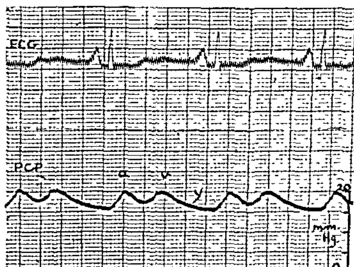


FIG 99 Pulmonary capillary venous pulse (PCP) in severe mitral stenosis in sinus rhythm

Mean = *17 mm. Hg* — *y* = *13 mm Hg*
a = 20 mm Hg — Ry/v ratio = 0 9
v = 20 mm Hg

capillary venous pulses and left atrial pulses (obtained by puncturing the left atrium through a bronchoscope)

The normal left atrial pulse shows a small "a" wave preceding ventricular systole, a sharp "x" descent, and "v" wave, due to atrial filling, of about the same height as the "a" wave, occurring in ventricular diastole. The "y" descent following the "v" wave is short and sharp. The mean pressure is around 5 mm. Hg normally, but is increased to ten if flow is high.

In mitral stenosis, the mean pressure is elevated, and the "a" wave dominant, sometimes startlingly so, although "v" is also increased in amplitude. The two other important abnormalities are the slow "y" descent and the diastolic gradient between left ventricle

that a true venous rather than a damped pulmonary artery pulse has been recorded. This should be done by timing the pulse waves with a synchronously recorded electrocardiographic trace (Figs. 99 and 101a). There is, of course, some delay in the pulmonary capillary venous pulse, all pressure waves showing a delay of 0·02–0·08/sec. when timed against corresponding waves from the left atrium (Epps and Adler, 1953).

Numerous direct studies of the left atrial pressure pulse have been made by puncturing the left atrium either via a bronchoscope, or via the paravertebral route (Björck *et al.*, 1953). The latter route may be hazardous, while bronchoscopic puncture may be difficult if the left atrium is small. Morrow *et al.* (1957) have correlated the direct left atrial pulse obtained by the former route with the state of the mitral valve at operation in 53 patients. They considered that the Ry/v ratio afforded the best method of distinguishing incompetence from dominant stenosis.

$$\text{The ratio} \quad \frac{\text{Rate of ``y'' descent}}{\text{Mean left atrial pressure}}$$

was also useful. But, when tachycardia was present, the duration of the "y" descent was shortened, tending to give a spuriously high figure. Morrow *et al.* (1957) noted that diastasis, the period immediately after the trough of the "y" descent, was always absent in dominant stenosis, the shallow "y" descent merging imperceptibly into the horizontal before the onset of the next "a" wave. They concluded that the severity of mitral incompetence in association with dominant stenosis could not be determined with certainty by any method of analysis of the left atrial pulse.

Left Heart Catheterization in Mitral Disease

Dickens *et al.* (1957) reported the results of simultaneous right and left heart catheterization in mitral disease. A polythene catheter was passed into the left atrium through a needle by the paravertebral route, and advanced into the left ventricle. In this way the gradient across the mitral valve was obtained, as well as the left atrial pressure. Pulmonary artery pressure and cardiac output were obtained by the standard technique for the right side of the heart.

Right heart catheterization combined with catheterization of the left atrium and left ventricle enable more extensive and precise haemodynamic measurements to be made than is possible by right heart catheterization alone. Left heart catheterization permits dye dilution curves to be recorded from the left atrium when dye is injected into the left ventricle, to assess the degree of incompetence (Woodward *et al.*, 1957; Marshall and Wood, 1958). The added complexity and risks of these manœuvres have yet to be shown to add significantly more useful diagnostic information than a thorough clinical, radiological and cardiographic assessment, supported by data obtained from right heart catheterization, and from dye dilution curves by the method of Korner and Shillingford (1955).

Records taken at thoracotomy show a ventricular filling pressure gradient across the mitral valve, which tends to be reduced when atrial fibrillation is present (Fig. 100). The simultaneous measurement of mitral valve flow and gradient should provide a better index of the degree of obstruction than the Gorlin formula or measurement of pulmonary

or absence of significant obstruction. It is only applicable when the pressure is significantly elevated, and interpretation may be difficult when there is sinus tachycardia or a very large left atrium. Careful measurement from the peak of the "v" wave to the end of the "y" descent, immediately before the beginning of the "a" wave of the next cycle is required and this is sometimes difficult in under-damped tracings. A technically faultless pulse tracing is therefore necessary for this measurement, and this is not always readily

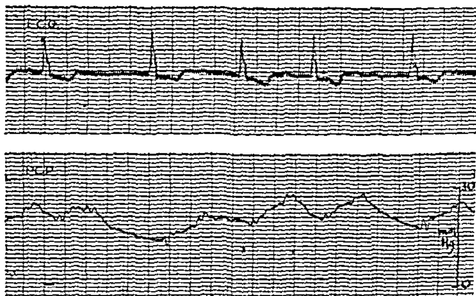


FIG. 101a. Pulmonary capillary venous pressure (PCP) in severe mitral stenosis in atrial fibrillation

Mean = 22 mm. Hg
v = 28 mm. Hg
y = 17 mm. Hg
Ry/v ratio = 0 65

obtainable, especially in cases with considerable narrowing of the small pulmonary arteries so that the catheter is difficult to wedge. The effects of respiration, which may be marked, must not be allowed to interfere with the tracing, and the tracing should be made

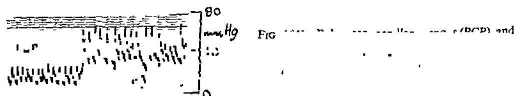


FIG ... (PCP) and

with the patient's breath held in full inspiration. Considerable swings in pressure occur with respiration in patients with severe stenosis, and this may be due to the inelasticity of the lungs which allows intrathoracic pressure transients to be transmitted to the vascular
bed. ... swing gives some indication of the severity of the
pulm... ...t the catheter has been correctly wedged can be
obtai... ...ement in pressure which occurs on slowly with-
drawing the catheter into the pulmonary artery (Fig. 101b). It is very important to ensure

TABLE 6

GRADE OF DYSPNOEA AND GRADE OF PULMONARY HYPERTENSION IN 73 PATIENTS SUBMITTED TO MITRAL VALVOTOMY

Radiological grade of pulmonary hypertension	*Grade of dyspnoea/Number of patients*			
	I	II	III	IV
0 (normal) .	2	9	5	0
I (moderate) .	0	14	15	0
II (severe) . .	0	6	20	2
	$x^2 = 7 \cdot 30$			

From Goodwin *et al* (1955)

siderosis. Haemoptysis due to pulmonary infarction occurs most commonly in cases with an extremely high vascular resistance and low output, or heart failure. It is usually embolic in origin from calf or pelvic vein thrombi. Thrombosis may arise *in situ*, in the pulmonary artery (Ball *et al.*, 1956) Systemic embolism, due to dislodgement of thrombus from the left atrium, occurs in 10–20 per cent of all cases; it is often recurrent and clearly related to atrial fibrillation.

Paroxysmal atrial fibrillation is not uncommon, giving rise to unpleasant attacks of palpitations, and when suddenly established at a rapid rate, may lead to acute heart failure. It is probable that many systemic emboli occur very shortly after the onset of atrial fibrillation, fresh clot being easily dislodged and carried into the circulation. Probably such clot either becomes rapidly organized and firmly adherent to the atrial wall, or is detached shortly after its formation

It is worth noting that atrial fibrillation is often late in onset in patients with severe pulmonary hypertension, perhaps because the left atrium is commonly only slightly enlarged. Conversely, fibrillation is invariable when the atrium is very large.

Anginal pain occurs in some patients, and has been thought to result from painful stimuli arising in stretched hypertensive pulmonary arteries. This is certainly not the case. The pain is due to cardiac ischaemia resulting from a low cardiac output, from previous coronary embolism (see Chapter 7), or from associated coronary artery disease.

Physical signs. In severe stenosis the appearance is characteristic, with pinched, blue facies and malar flush. When the output is low, the extremities are cold, blue, and the arterial pulse small In most cases, however, the pulse is unremarkable. The jugular venous pressure is frequently normal, but in hypertensive cases shows a dominant "a" wave. The "y" descent is sharp unless tricuspid stenosis is also present. When atrial fibrillation has occurred there is a small systolic (cv) wave, which becomes much larger if tricuspid insufficiency occurs. The cardiac impulse is dominated by the right ventricle,

vascular pressures, since the latter are influenced by the pulmonary blood flow and arteriolar resistance, and the indirect left atrial pressure measurement does not always accurately reflect the degree of mitral obstruction.

Although direct estimation of mitral valve gradient and flow provides useful additional information, it is rarely necessary except in particularly difficult cases. Furthermore, left heart catheterization is not without risk.

The Clinical Syndrome of Mitral Stenosis

Symptoms. The cardinal symptoms are dyspnoea, "bronchitis", and haemoptysis, and all are related to the degree of pulmonary venous hypertension and the presence of pulmonary congestion. Fatigue is common, and results from a reduced cardiac output.

Dyspnoea, principally on exertion, is due to rigid and inelastic lungs, and tends to be progressive as the effects of chronic venous hypertension on the lungs increase Attacks of paroxysmal dyspnoea sometimes amounting to pulmonary oedema, are not uncommon, and are usually precipitated by any stress which causes undue tachycardia, especially emotion and exercise. Paroxysmal dyspnoea is also seen in pregnancy, when the increased demands on the circulation, and salt retention, are added hazards. Attacks of paroxysmal orthopnoea occurring when the patient slips down flat in bed while asleep, may be troublesome. The degree of dyspnoea on exertion is roughly proportional to the severity of the mitral obstruction (Goodwin *et al*, 1955), provided that other factors such as anaemia, infective endocarditis, pulmonary infection, and uncontrolled atrial fibrillation are excluded The severity of the dyspnoea is also proportional to the degree of pulmonary arterial hypertension, although the appearance of dyspnoea is delayed in some cases in which the arteriolar resistance is extreme.

Holling and Venner (1956) noted a closer direct relation between pulmonary artery pressure and dyspnoea than between pulmonary capillary venous pressure and dyspnoea, perhaps because the increased arteriolar resistance provides a more rigid framework for the lungs, which require more work to ventilate them. These findings are supported by personal experience, for Goodwin *et al* (1955) also found a direct relationship between the degree of dyspnoea and the degree of pulmonary arterial hypertension (Table 6)

Attacks of "bronchitis" with wheezing and infected sputum are common and are probably related to reduced resistance to infection of the congested lungs. There is usually no impairment of blood gas exchange. Pulmonary congestion is always an important factor in promoting such attacks for they usually cease after successful valvotomy with reduction in left atrial pressure.

Haemoptysis, according to Wood (1956), may be of several types: sudden profuse haemorrhage, blood streaked or viscid infected sputum; blood stained frothy sputum associated with pulmonary oedema; and small frank haemoptysis due to pulmonary infarction. The first type (pulmonary apoplexy) is thought to be due to rupture of a small intrapulmonary bronchial vein, or varicose bronchopulmonary anastomotic vessel. It may be severe and repeated and give rise to considerable anaemia in a minority of cases. This type of haemorrhage is perhaps more common in early cases, for after many years of subjection to a high venous pressure, the vessel walls thicken and resist rupture so that haemoptysis becomes less likely. Repeated haemoptyses are often associated with haemo-

become equal. In mild cases the murmur is short, and ends as soon as the pressures equalize.

Thus the severity of the stenosis can be gauged by the intensity of the first heart sound, by the length of the diastolic murmur, and sometimes by the position of the opening snap (Fig. 102). Indirect auscultatory signs of mitral stenosis consist of alterations in the second heart sound, and of certain added sounds.

When substantial pulmonary hypertension is present, the pulmonary component of

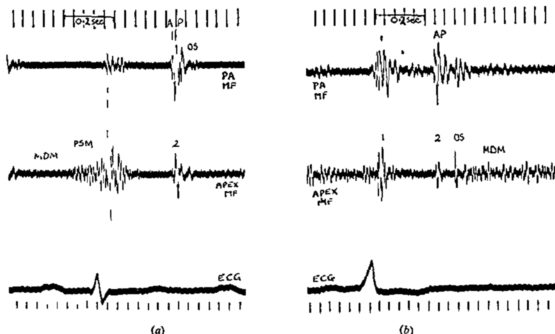


FIG 102. Phonocardiogram in severe mitral stenosis· (*a*) in sinus rhythm, (*b*) in atrial fibrillation

1 = 1st heart sound
2 = 2nd heart sound { A = aortic valve closure; P = pulmonary valve closure }
PSM = presystolic murmur
MDM = mid-diastolic murmur
OS = opening snap
PA = pulmonary artery area
MF = medium frequency
Apex = apical cardiac impulse

the second heart sound is accentuated and the split narrow. In extreme cases, with marked enlargement of the main pulmonary artery, an early systolic click may be heard, and sometimes a faint short high-pitched early diastolic murmur is present over the pulmonary artery, signifying pulmonary valvular incompetence This murmur may sometimes be differentiated from an aortic incompetent murmur by its accentuation on inspiration. When right atrial hypertension is considerable a fourth heart sound may be heard over the right ventricle: it arises, of course, from the right and not from the left, atrium.

A third heart sound is sometimes heard in mitral disease. When present at the apex,

which produces a diffuse sternal lift; the left ventricular thrust is absent except in mild cases or those associated with appreciable incompetence, aortic valve disease, or systemic hypertension. In some cases a diastolic thrill may be felt at the apex.

Auscultation is of the greatest importance in assessing the type and severity of mitral valve disease. The important signs of mitral obstruction are the accentuated and delayed first heart sound, the *opening click or snap of the mitral valve, and the rumbling pre*-systolic and mid-diastolic murmurs.

The first sound is accentuated because the late diastolic atrio-ventricular pressure gradient holds the mitral cusps wide open until the end of diastole, so that when the ventricle contracts they meet sharply together. The first sound is delayed slightly because the left ventricle spends the first 0·01 sec. of systole raising its pressure to atrial level. When atrial fibrillation is present the delay is inversely related to the length of the preceding cycle (Messer *et al.*, 1951).

The opening snap, as its name implies, is related to the opening of the mitral valve. It is usually considered to be due to the aortic cusp being propelled into the left ventricle under the thrust of the raised left atrial pressure (Wood, 1956), but its presence in cases with calcified immobile cusps has led to the suggestion that the sound is made by the entire valve as it moves deep into the left ventricle (Leatham, 1958). This view would harmonize with the observation that the snap is dull and soft when the valve is rigid, and loud and clear when pliable. It occurs at the summit of the "v" wave of the venous pulse, and is heard with maximal intensity internal to the apex and down the left sternal border, being loudest in expiration. It can thus be differentiated from the pulmonary component of the second heart sound which is most obvious in inspiration (Leatham, 1958)

The presence of an opening snap is vital to the diagnosis of mitral obstruction If it is absent, some doubt may be cast upon the diagnosis, but care must be taken to ensure that a very early snap due to severe stenosis has not been missed. An exception to this rule is said to be the presence of aortic incompetence when the regurgitant jet may interfere with the forward movement of the outer cusp (Wood, 1956)

The relation of the opening snap to the second heart sound has some value as a guide to the severity of the obstruction The earlier is the snap the tighter is the stenosis (Wells, 1954), because the interval between aortic valve closure and the snap is inversely proportional to the height of the left atrial pressure (Messer *et al.*, 1951). The snap is usually 0·03 to 0·14/sec. (average 0·07) after aortic valve closure (Mounsey, 1953). However, factors other than left atrial pressure influence the timing of the snap, which tends to be late if aortic pressure is high and earlier if it is low (Julian and Davies, 1957). Leatham (1958) considered that the factors involved were too numerous to allow serious use of the timing of the snap as an index of the severity of the stenosis. In the author's view it is principally of value when taken in conjunction with the other physical signs.

The diastolic murmur follows the opening snap, and is low pitched and rumbling in character. It is due to blood flowing through the obstructed valve during atrial systole. When sinus rhythm is present, there is presystolic accentuation due to *active atrial con*-traction, and the murmur has a crescendo quality. When atrial fibrillation has occurred, the presystolic crescendo is abolished, leaving the mid-diastolic rumble. The length of the murmur is of great importance, in severe cases being full length and extending up to the first heart sound of the next cycle, for the diastolic pressures in atrium and ventricle never

become equal. In mild cases the murmur is short, and ends as soon as the pressures equalize.

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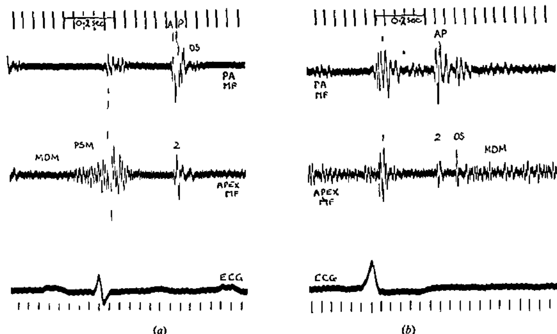


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Radiological features include lack of pulsation of the affected main branch, persistent pleural effusion, and occasionally calcification in the pulmonary artery (Chapter 5).

Aortic stenosis and incompetence are the most frequently associated valve lesions, and apart from producing additional murmurs, cause enlargement of the left ventricle. Tricuspid stenosis, if severe, damps out the typical right ventricular impulse and may permit the left ventricle to be felt. The tricuspid stenotic murmur resembles the mitral, but increases markedly on inspiration: it may be conducted to the apex, however The presence of tricuspid stenosis should be suspected when the jugular venous pulse shows an "a" wave which is out of proportion to the degree of right ventricular enlargement and intensity of pulmonary valve closure: the "y" descent is, of course, slow. Tricuspid incompetence is common in the presence of atrial fibrillation, but an explanation for its occurrence must always be sought. It is usually the result of severe pulmonary hypertension and failure of the right ventricle, but may occur from general myocardial insufficiency, or in association with tricuspid stenosis. Study of the venous pulse in tricuspid stenosis before and after the onset of fibrillation, and of the pathological anatomy of the stenosed tricuspid valve, suggests that tricuspid stenosis is almost invariably associated with incompetence, which becomes greater when active atrial contraction ceases (Goodwin, *et al.*, 1957; Hollman, 1957) The "y" descent is slow when tricuspid incompetence is due to stenosis but rapid when due to other causes The pansystolic murmur of tricuspid incompetence, heard at the tricuspid area, and increasing in inspiration, is usually present

Occlusive thrombi in the left atrium may be sessile or pedunculated. When sessile, they merely increase the degree of left atrial obstruction. They are much commoner with atrial fibrillation than with sinus rhythm, and multiple emboli may complicate the picture The thrombus may show patchy calcification which is visible radiologically. The incidence of occlusive atrial thrombi is difficult to establish, but Wallach *et al.* (1953) estimate the overall incidence at between two and thirteen per cent, basing their figures on four series collected from the literature

Ball-valve thrombus may be suspected in the presence of variable auscultatory signs of mitral stenosis which change with position; attacks of syncope; showers of systemic emboli; and cardiac pain. All these events may, of course, occur with severe mitral stenosis alone, but their co-existence in the same patient should always arouse the suspicion of mass thrombus (Evans and Benson, 1948). The occurrence of syncope and the disappearance of the murmur in certain postures may be attributed to the tumour swinging on its pedicle to block the mitral valve. Wallach *et al* (1953) consider that death is usually caused by progressive obstruction to left ventricular inflow, which may occur from obstruction to the valve by the mass, which fills the left atrium almost entirely, or by spread of the thrombus to occlude the pulmonary veins. These two mechanisms are probably often associated.

Although the diagnosis may be suspected clinically, it is difficult to prove, the haemodynamics being identical with those of mitral valve disease.

A good venous angiogram, or pulmonary arteriogram, to outline the left atrium is required to make the diagnosis, which is confirmed by finding a substantial filling defect. Diagnosis is important, for removal of the thrombus may be lifesaving. This may not be possible without open cardiotomy with some form of assisted circulation, so that exploratory thoracotomy on a mere suspicion is not adequate.

it probably arises from the left ventricle, and results from rapid filling. This, of course, denies appreciable mitral obstruction, and usually suggests the presence of substantial incompetence or left ventricular failure from some associated disorder. The third sound may be distinguished from the opening snap by its dull quality and localization to the apex. It occurs later than the snap, coinciding with the end of the "y" descent of the venous pulse. A right ventricular third heart sound may be heard in the presence of tight stenosis when right ventricular failure is present.

Modifications in the typical clinical picture of mitral stenosis The classical signs may be modified for the following reasons:

1. The presence of mitral incompetence,
2. Calcification of the mitral valve,
3. Pulmonary vascular disorder,
4. Associated valve lesions,
5. Occlusive thrombus in the left atrium.

The presence of associated mitral incompetence damps the intensity of the first heart sound, and produces a pan-systolic murmur at the apex, radiating to the axilla, and diminishing on inspiration. The left ventricle is enlarged if the incompetence is appreciable. When incompetence dominates stenosis a third heart sound is present, and the mid-diastolic murmur short. The arterial pulse is jerky in character and small in volume The incompetent murmur can be distinguished from that due to tricuspid incompetence, for the latter is maximal at the tricuspid area and increases on inspiration.

Heavy calcification of the mitral valve is usually associated with some incompetence, though not invariably so It damps the first heart sound and opening snap It may be suspected clinically, but radiology is required for confirmation (Chapter 5)

Pulmonary vascular disorder is most frequently manifested by an extreme degree of pulmonary arterial hypertension When this occurs the right ventricle may be very large and the left ventricle rotated around towards the left axilla When left atrial inflow is restricted by extreme arteriolar constriction, the first sound may be soft, the snap quiet and the diastolic murmur virtually inaudible. This so-called "silent" type of mitral stenosis can be most misleading, and resemble idiopathic pulmonary hypertension, for the signs of pulmonary hypertension (Chapter 4) dominate the clinical picture. However, the diastolic murmur can usually be brought out by exercise, and heard with the patient lying on the left side, while the X-ray may reveal tell-tale evidence of pulmonary venous hypertension (Chapter 5)

Thrombosis of the major pulmonary arteries is an infrequent but important complication of mitral stenosis indeed, mitral stenosis is one of the commonest causes of the syndrome (Ball *et al.*, 1956) Thrombosis is usually the result of repeated peripheral emboli, and is often accompanied by occlusion of small pulmonary vessels also A certain proportion of cases are thought to arise *in situ*, on the basis of atherosclerosis in the pulmonary artery, aided by dilatation of the main branches, low cardiac output, and high pulmonary pressure. The effect of major thrombi is to cause progressive and relentless right ventricular failure, sometimes punctuated by episodes of syncope, fever, and haemoptysis due to pulmonary infarction. It should be suspected whenever unexpected progressive deterioration and right ventricular failure assail a patient with mitral stenosis.

Radiological features include lack of pulsation of the affected main branch, persistent pleural effusion, and occasionally calcification in the pulmonary artery (Chapter 5).

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Myxoma of the left atrium produces a similar picture, and will be discussed late this chapter.

Clinical Assessment of the severity of mitral stenosis. The haemodynamic correlati have already been discussed. Certain clinical points require further mention, as they sist bedside assessment of the severity of the mitral disease. The degree of dyspnoea exertion correlates positively with the degree of stenosis, provided that appreciable mit incompetence is absent, (Table 7). The radiological degree of pulmonary hypertens also correlates positively with the severity of the stenosis (Goodwin *et al.*, 1955)

TABLE 7

GRADE OF DYSPNOEA AND VALVE SIZE IN 75 PATIENTS SUBMITTED TO MITRAL VALVOTOMY

Valve orifice size	*Grade of dyspnoea/Number of patients*			
	I	II	III	IV
>2 cm.	1	0	0	0
1·5–2 cm	1	0	3	0
1–1 5 cm.	1	17	7	3
1 cm	0	12	30	0
	$x^2 = 6{\cdot}50$			

The radiological assessment of pulmonary hypertension has been fully discussed in Chapt 5 and will not be further considered here The radiological appearances correlate rath better with the systolic pulmonary artery pressure, than with the arteriolar resistan (Table 8).

TABLE 8

CATHETER GRADE OF PULMONARY HYPERTENSION AND RADIOLOGICAL GRADE OF PULMONARY HYPERTENSION IN 37 PATIENTS

Radiological grade of pulmonary hypertension	*Catheter grade of pulmonary hypertension/ Number of patients*		
	0	*I*	*II*
0 (normal)	1	5	0
I (moderate)	1	11	3
II (severe)	0	1	15

The radiological changes may be more valuable guide to pulmonary vascular disease than a single measurement of pulmonary artery pressure, which is influenced by cardiac output and other factors. The pulmonary resistance is not, of course, a direct measurement, but a derivation from two variables.

In practice the severity of the stenosis can be gauged at the bedside from the history, the auscultatory findings at the mitral area, the clinical signs of pulmonary hypertension, and the radiological evidence of venous and arterial hypertension. The cardiogram is of limited value (Chapter 7). In most cases cardiac catheterization is therefore not required. The foregoing remarks on clinical assessment of severity apply to pure or dominant stenosis, with little or no incompetence. The presence of significant incompetence modifies the haemodynamic and clinical picture, and upsets the correlations from the standpoint of assessment of valve size: it will be discussed later.

Effects of mitral valvotomy. Mitral valvotomy is capable of exerting a profound effect upon the haemodynamics in mitral stenosis, and especially upon the pulmonary circulation. In successful cases in which a good valve split (3–4 cm diameter) has been obtained, there is a fall in mitral valve gradient, in left atrial pressure, pulmonary artery pressure, and pulmonary vascular resistance, and a rise in cardiac output. The immediate results of valvotomy have been studied at thoracotomy by Zoob *et al.* (1958) They found that if the split was 1·5 cm. or more there was an appreciable fall in left atrial pressure and an increase in left ventricular systolic pressure, suggesting a rise in output. When incompetence was also present, the valvotomy reduced the left atrial pressure in only half the cases. The effect on pulmonary artery pressure was variable, but there was usually a fall proportional to that in left atrial pressure when the latter was considerable But when the initial left atrial pressure was lower the fall in pulmonary artery pressure was less marked They considered that there was no immediate fall in pulmonary vascular resistance. Goodale *et al.* (1955), however, in studies made six months to one year after valvotomy, noted a striking fall in arteriolar resistance which was proportional to the initial level. Presumably, therefore, the arteriolar vasoconstriction takes time to wear off, as would be expected from the hypertrophied media of the pulmonary arterioles.

Donald *et al* (1957) studied 28 patients before and from 17 to 51 months after, valvotomy. In the great majority the pulmonary artery and pulmonary capillary pressures fell, and the pulmonary ventilation at rest and on exercise was greatly reduced. The resting oxygen uptake was also reduced, probably as a result of the diminished work of breathing achieved by relief of pulmonary venous and arterial hypertension. Although the work of the right ventricle was usually diminished after operation, the resting cardiac output was reduced, a finding which is not in sympathy with the other changes and is not readily explicable.

There is little doubt, however, that successful valvotomy is followed by return towards normal of the haemodynamic abnormalities, and reduction in symptoms The auscultatory signs also diminish, but only if the surgeon achieves a valve diameter of 3–4 cm. Cardiographic signs of right ventricular hypertrophy regress, as do the radiological signs of pulmonary venous, and to a much lesser extent of arterial, hypertension (Goodwin *et al.*, 1955) (Chapter 5).

Unfortunately, re-stenosis may occur (Belcher, 1960), especially if the valvotomy was a poor one. Haemodynamic abnormalities then recur, and a second valvotomy may be necessary (Wilcken, 1960).

The fall in pulmonary venous pressure and in pulmonary arteriolar resistance which occurs in the first year after successful valvotomy is of course excellent evidence that arteriolar vasoconstriction is precipitated by a raised left atrial pressure.

MITRAL INCOMPETENCE

Serious mitral incompetence reflects graver valvular damage than simple stenosis, and thus it is common to find rigidity, subvalvular stenosis, and calcification in association. Some degree of mitral stenosis is usually present, and may be quite severe, the valve being so disorganized as to consist merely of a fixed, narrow, rigid orifice which cannot open or close fully.

In some cases almost pure mitral incompetence exists, and this is usually due to shrivelling of one cusp, which fails to meet the other cusp, and so allows free regurgitation.

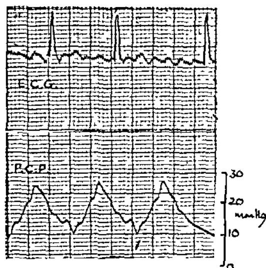


FIG. 103. Pulmonary capillary venous pulse (PCP) in mitral incompetence
v = 26 mm. Hg
y = 10 mm Hg
Ry/v ratio = 1 6
(Electrocardiogram shows atrial fibrillation)

Actual stretching of the mitral valve ring is not common in chronic rheumatic mitral disease.

Haemodynamics. When there is little obstruction to left ventricular inflow, the ventricle fills rapidly because of the high pressure obtaining in the left atrium caused by the regurgitant jet from the previous cycle The left atrium is therefore dilated, and the left ventricular stroke volume increased because of the additional burden of maintaining a normal forward output through the aortic valve in addition to the regurgitant jet. The left atrial pressure is very high during ventricular systole, especially in the early phase (Wynn *et al.*, 1952). It falls rapidly to ventricular level in diastole so that the mean pressure is lower than in mitral stenosis. The "y" descent of the venous pulse is sharp in the absence of obstruction to left ventricular filling and the Ry/v ratio is above 1·5 (Owen and Wood, 1955) (Fig. 103).

Marshall and Wood (1958) have recently contrasted the findings in pure incompetence

and pure stenosis In the former they found a high peaked "v" wave, absent "x" descent, and rapid "y" descent. The presystolic mitral valve gradient was absent. In combined stenosis and incompetence, the gradient was less than in pure stenosis. The "v" wave was smaller, and the "y" descent slower, than in pure incompetence.

The degree of pulmonary arterial hypertension is usually less than in mitral stenosis, because of the lower mean pulmonary venous pressure. The presence of severe arterial [illegible] appreciable stenosis [illegible] with pure in- [illegible] to occur than in stenosis, for a reduced diastolic period produces less increase in left atrial pressure.

Clinical features. In mitral incompetence, when stenosis is mild or absent, the symptoms are usually far less urgent than in severe mitral stenosis, dyspnoea being less,

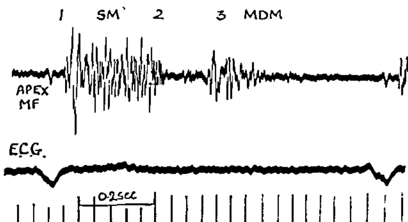


Fig 104 Phonocardiogram in severe mitral incompetence.

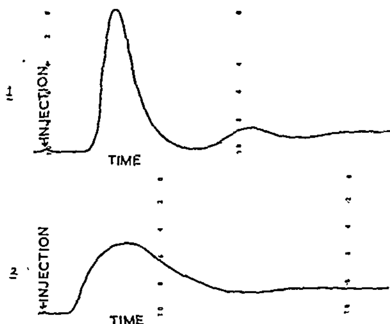
1 = 1st heart sound
2 = 2nd heart sound
3 = 3rd heart sound
MDM = mid-diastolic murmur
Apex = apical cardiac impulse
MF = medium frequency
SM = pansystolic murmur

pulmonary oedema unusual, and systemic embolism infrequent Tiredness has been stressed as a feature, but is probably of no great diagnostic significance

The clinical signs include a small, jerky arterial pulse, hyperdynamic left ventricular impulse, with only slight right ventricular enlargement, and the characteristic pansystolic murmur at the apex, conducted to the axilla, and decreasing on inspiration. The murmur also diminishes when the peripheral resistance is reduced by inhalation of amyl nitrite (Barlow and Shillingford, 1958). The first heart sound is soft, and there is usually a short, faint mid-diastolic murmur and a third heart sound (Fig. 104) Severe mitral incompetence is frequently accompanied by tricuspid incompetence.

The cardiogram shows left, rather than right, ventricular hypertrophy, and the left atrium is frequently very large. Atrial fibrillation is common, but not invariable except in very severe cases (Chapter 7)

The assessment of combined mitral stenosis and incompetence. When appreciable mitral stenosis co-exists, the assessment of the dominant lesion or the amount of incompetence may be difficult. Assessment is best made by a combined clinical and haemodynamic study, supplemented by the use of dye dilution techniques. Clinically, the presence of a long mid-diastolic murmur, and signs of considerable pulmonary hypertension are good pointers to the presence of appreciable mitral stenosis Significant incompetence does not usually exist with a very small mitral orifice of less than 1 cm., but can be considerable with larger valves between 1 and 2 cm. McDonald *et al.* (1957) found significant regurgitation to be exceptional when the valve was less than 0·8 cm² and usually of moderate severity with valves of 0·9–1·0 cm². With valves larger than this, incompetence tended to be the predominant lesion in patients with clinically significant mitral valve disease.



FIG

In the presence of severe mitral stenosis an apical pansystolic murmur suggests associated incompetence, but this is unlikely to be appreciable if the first sound is loud, the opening snap early, and the diastolic murmur long Absence of left ventricular enlargement is also good evidence against important incompetence, and conversely, the presence of left ventricular enlargement in a patient with mitral stenosis but without aortic valve disease suggests the possibility of significant mitral incompetence, which can occasionally occur in the absence of a systolic murmur (McDonald *et al.*, 1957) although this is rare.

The presence of heavy valve calcification and a very large left atrium suggest incompetence, but these points should not be allowed to outweigh definite clinical signs of pure stenosis

Assessment from the form of the left atrial pulse may be fallacious as has already been shown, although an Ry/v ratio of more than 1·5 suggests little stenosis, and therefore, if signs of mitral valve disease are severe, important incompetence.

Dye dilution techniques have been used to assess incompetence (Korner and Shillingford, 1955; Shillingford, 1958; Marshall and Wood, 1958).

Injection of indicator dye into the pulmonary artery gives a deformed dye dilution curve when recorded by an ear oximeter. The normal rapid exponential fall off is replaced by a shallow, slow decline, and the peak is smaller. This is due to the dilution and delay in dye particles reaching the photo-electric cell caused by the regurgitation of blood back and forth across the mitral valve. The appearance time is shortened. The amount of regurgitation can be quantitated by replotting the curve on semi-logarithmic paper, and taking the ratio of the appearance time of dye at the oximeter to the spread of the curve

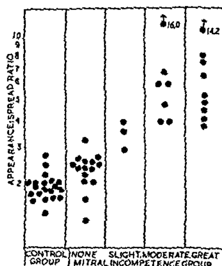


Fig 105b The assessment of mitral incompetence by dye dilution and clinical methods. The relation between appearance time/spread of

at one tenth of the maximum concentration Assessment in this way correlates quite well with the clinical assessment of incompetence (Shillingford, 1958) (Figs 105a and b).

An alternative method has been described by Wood and Woodward (1957) Following injection of dye into the pulmonary artery, the ratio of the least concentration to the systemic recirculation concentration of dye is calculated from dilution curves recorded simultaneously from the ear and radial artery. Well-marked recirculation peaks were detected in the radial artery curves in normal subjects or those with pure or dominant mitral stenosis, but not in those with pure or dominant incompetence.

Dilution curves recorded from the left atrium after injection of dye into the left ventricle have yielded rather disappointing results (Woodward *et al.*, 1957). As has already been said, the advantage of left-sided dye dilution curves over the simple pulmonary artery injection has yet to be shown

The diagnosis is assuming great importance, since the introduction of techniques of mitral valvuloplasty under direct vision using total cardio-pulmonary by-pass (Guidry *et al.*, 1958; Lillehei *et al.*, 1958)

THE MEDICAL TREATMENT OF MITRAL VALVE DISEASE

In mitral stenosis, atrial fibrillation must be controlled by digitalis, respiratory infections by antibiotics, and anaemia corrected if present. Pulmonary artery thrombosis and infarction require anticoagulant therapy A low salt diet and diuretic therapy will be required for congestive heart failure. When operation is impracticable or ineffective, and patients remain breathless, attempts have been made to reduce pulmonary hypertension and congestion by means of vasodilator drugs. Such attempts however, are doomed to failure, for the basic cause of the hypertension and congestion, the obstructed valve, has not been influenced Personal experience with ganglionic blocking agents in mitral stenosis has shown that these drugs are quite useless in treatment. This is not surprising,

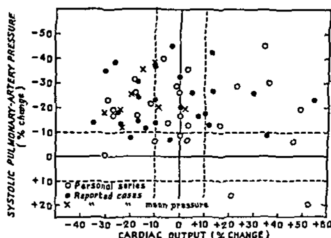


FIG. 106 The effect of hexamethonium on pulmonary artery pressure and cardiac output in 60 cases of mitral stenosis The top right quadrant shows the cases in which a fall in pulmonary arterial pressure is accompanied by a rise in cardiac output.

for the reasons stated above, but also because of the variable effect on cardiac output My colleagues and I have shown in acute observations of our own, and from the data of others, that the cardiac output falls in 30–50 per cent of patients, and although this lowers pulmonary arterial and venous pressures, it does not help the patients (Goodwin *et al*, 1958). In a minority of cases, hexamethonium lowers the pulmonary artery pressure, and increases cardiac output, suggesting pulmonary vasodilatation (Fig. 106), but this has never proved beneficial in treatment, with the possible exception of acute pulmonary oedema (Davies *et al.*, 1954). It is not now considered advisable to give hexamethonium routinely in acute pulmonary oedema, however, because in patients with a tight mitral valve and low fixed cardiac output, peripheral vasodilatation might well exceed pulmonary vasodilatation, with resultant fall in central venous filling pressure and cardiac output. This could obviously be dangerous, since such patients are probably dependent upon intense peripheral vasoconstriction to maintain their output (Goodwin *et al.*, 1958).

But in acute left ventricular failure, without obstruction to the mitral valve, hexamethonium is of great value.

In mitral incompetence, hypotensive drugs should theoretically be of benefit since the regurgitant jet is diminished where the peripheral resistance is lowered. Clinically, reduction in the systolic murmur of incompetence is noted when the blood pressure is low. It is doubtful if such treatment is warranted in patients with normal systemic blood pressure, but may be considered when appreciable systemic hypertension and mitral incompetence co-exist The development of newer surgical techniques may permit effective surgical treatment in the future



FIG 107 Autopsy specimen showing myxoma entirely filling the left atrium (viewed from above)

LEFT ATRIAL OBSTRUCTION

True myxoma of the left atrium behaves in a very similar fashion to a large occlusive thrombus complicating mitral stenosis, and the differential diagnosis may only be possible at thoracotomy or post-mortem. This tumour usually occurs as a polypoid mass growing from the left side of the atrial septum in the region of the fossa ovalis. It is smooth, shining, and gelatinous, and presumably represents a true new growth, but may possibly

be due on occasions to myxomatous degeneration in a thrombus (Fig. 107) The haemodynamic effects upon the pulmonary circulation are identical with those of mitral stenosis, as are the auscultatory signs, even an opening snap having been noted (Chin and Ross 1957). Murmurs are often inconsistent and variable and, evidence of a general disturbance consisting of hyperglobulinaemia, raised E.S R. fever, and anaemia, may be present (MacGregor and Cullen, 1959).

As with massive thrombi, a good angiogram may be essential for diagnosis (Goldberg *et al.*, 1952). Detection is important, since removal may be lifesaving, and often requires open cardiotomy with hypothermia, or cardio-pulmonary by-pass. The tumour has to be handled with care, as fragments may easily become detached, and give rise to emboli.

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CHAPTER 9

CONGENITAL HEART DISEASE

BY JOHN GOODWIN

IN this chapter the pulmonary circulation in various forms of congenital heart disease will be discussed. No attempt will be made to give a full account of congenital heart disease except in so far as it influences the circulation to the lungs

With this approach, the following classification is proposed·

1. Lesions which impede the flow of blood to the lungs by obstructing ventricular outflow (pulmonary oligaemia):
   (*a*) *Obstruction to the right ventricular outflow tract:*
   Infundibular pulmonary stenosis.
   Vulvular pulmonary stenosis.
   (*b*) Obstruction to one or more pulmonary artery:
   Unilateral pulmonary stenosis.
2. Lesions in which the circulation to the lungs is provided by vessels other than pulmonary arteries (bronchial artery syndromes).
3. Lesions associated with excessive pulmonary blood flow (pulmonary plaeonaemia) due to left to right central shunt, and pulmonary hypertension.
4. Lesions associated with pulmonary hypertension and reversed (right to left) central shunt (the Eisenmenger syndrome).
5. *Lesions in which the arrangement of blood vessels is abnormal: pulmonary arterio*-venous connection; anomalous venous drainage; transposition of the great vessels.
6. Lesions associated with obstruction to the left side of the heart.

Some of these groups will overlap, as will be apparent from the subsequent descriptions.

1. PULMONARY STENOSIS—INFUNDIBULAR AND VALVULAR

Tetralogy of Fallot

The four components making up the Tetralogy are pulmonary stenosis, ventricular [illegible] ·le. Characteristically, [illegible] ular level, and severe [illegible] blood away from the lungs into the aorta and to the obstruction to flow into the pulmonary artery. The overriding aorta facilitates the right to left shunt, which is proportional to the severity of the pulmonary stenosis. The cardinal clinical features are marked central cyanosis, polycythaemia, dyspnoea, underfilled lungs, and signs of pulmonary stenosis. It is now realized that there is a wide spectrum of severity in the Tetralogy, depending on the size of the right

ventricular outflow tract and the degree of pulmonary stenosis, some cases showing little or no cyanosis, and signs of mild pulmonary stenosis, while others have intense cyanosis, grossly dextroposed aorta, and severe stenosis and hypoplasia of the pulmonary artery.

In some cases the dextroposition may be so marked as to constitute partial transposition The magnitude of the right to left shunt depends more upon the relative resistances in the pulmonary and systemic circulation than upon the position of the aortic root however, and when the resistance offered by the stenosis is of the same order as that of the peripheral systemic resistance, a left to right shunt is also present. When the stenosis is mild, and the aortic root only slightly over-riding, the shunt may be solely left to right, and cyanosis absent, so that the lesion is for all practical purposes a simple ventricular septal defect with mild pulmonary stenosis. An appreciable fall in oxygen saturation on exercise permits differentiation Other variations occur in which the main pulmonary arteries to one or both lungs may be hypoplastic or even atretic. All these factors have a direct bearing upon the pulmonary circulation.

The typical Tetralogys exemplified by the type of lesion in which pulmonary stenosis is associated with a right to left shunt, central cyanosis and polycythaemia. These factors all influence the pulmonary circulation and will now be discussed.

The stenosis is infundibular in about 60 per cent of cases and valvular, or combined *valvular and infundibular, in the remainder. The site of the stenosis influences the size of* the major pulmonary arteries. Thus, in the majority of cases infundibular stenosis is associated with a small main pulmonary artery and right and left main branches, the small main trunk producing the characteristic concave left cardiac border on X-ray. When valvular stenosis alone is present, the main trunk, and sometimes the left main branch, but never the right main branch, are enlarged.

The pulmonary arterial tree distal to the valve may be abnormal. The distal and peripheral arteries are small and thread-like. Rich (1948) reported thrombotic occlusion of small pulmonary vessels in 90 per cent of autopsied cases. Presumably this is the result of increased blood viscosity due to polycythaemia, and of reduced pulmonary flow and pressure. Ferencz (1959) found no correlation between the degree of polycythaemia, the age of the patient, and the extent of the vascular lesions. But she did find that a history of attacks of intense cyanosis and dyspnoea was twice as frequent in cases with severe lesions as in those with little or no vascular disorder. Possibly the thromboses occur when the pulmonary circulation is greatly slowed during the cyanotic attack. The paucity of blood *in the vessels renders the lungs unduly translucent on X-ray. Absence of one main pul-*monary artery, or extreme hypoplasia of one or both arteries may occur In three of four cases reported by Nadas *et al.* (1953) absence of the left pulmonary artery was associated with dilatation of the right main artery and pulmonary vascular engorgement at the right hilum, the fourth patient having dextrocardia and absence of the right main pulmonary artery with dilatation of the left. Absence of the left main pulmonary artery is probably the only circumstance in which pulmonary valvular or infundibular stenosis is associated with an enlarged right main branch In some patients, the pulmonary arteries are better developed in one lung than the other, giving unequal pulmonary vascularity. Patent ductus arteriosus, helping to improve pulmonary flow, is present in some cases. Bronchial arteries are often prominent in patients with pulmonary atresia for they enlarge in response to the insufficient pulmonary blood flow.

A right-sided aortic arch occurs in 25 per cent of cases, as does a double superior vena cava, but not necessarily in association.

Haemodynamics. The pulmonary arterial pressure is reduced proportionately to the severity of the stenosis, the right ventricular systolic pressure being equal to that of the [illegible] septal defect (Fig. 108) Since [illegible] gs from the pulmonary artery [illegible] an intermediate zone of pressure between the body of the right ventricle and the pulmonary artery. This intermediate zone represents the infundibular chamber above the obstruction. The systolic pressures in the pulmonary artery and infundibular region are closely similar, the diastolic pressure falling in the infundibular chamber and the systolic pressure rising sharply in the body of the right ventricle When valvular and infundibular stenosis are combined, a pressure gradient occurs both between the pulmonary artery and the infundibulum and between

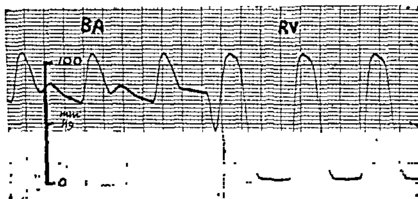


FIG [illegible]

the infundibulum and body of the right ventricle (Connolly *et al*, 1953) (Fig. 109a). When valvular stenosis alone is present, a sudden pressure gradient occurs localized to valve level, no intermediate pressure zone being present. Just before the valve is reached the pulse contour in the pulmonary artery shows a negative dip in systole, due to the venturi effect (Fig. 109b)

The circulation to the lungs is further profoundly influenced by variation in tone of the right ventricular outflow tract Sir Russell Brock (1955, 1956) has demonstrated that after pulmonary valvotomy a secondary stenosis develops in the infundibular region This has been attributed to increase in tone of the muscular infundibulum. Wood (1958a) has produced evidence to show that infundibular "spasm" may be the cause of the syncopal attacks and hypercyanosis which occur in 20 per cent of patients with the Tetralogy.

During these attacks the systemic blood pressure remains unchanged, the arterial saturation falls precipitously, the pulmonary artery pressure is very low, and the pulmonary ejection murmur disappears. The jugular venous pressure does not rise. Maintenance of

systemic blood pressure excludes peripheral vasodilatation as the cause. The disappearance of the murmur and increase in right to left shunt indicate almost total interruption of pulmonary blood flow. This could be due either to pulmonary vasoconstriction or to

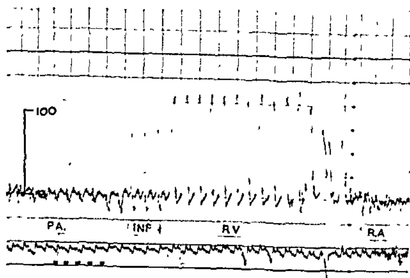


FIG. 109a Pressure gradients in combined valvular and infundibular stenosis:
P A = pulmonary artery
Inf. = infundibulum of right ventricle
R.V. = body of right ventricle
(Courtesy of Dr A Hollman)

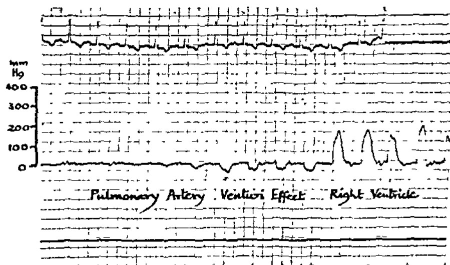


FIG. 109b Pressure gradient at valve level in pulmonary valvular stenosis.

infundibular contraction. The former can be excluded by the fall of pulmonary arterial pressure. Under anaesthesia with cyclopropane and oxygen, cyanosis is slight, and the pulmonary artery pressure at its usual level. When cyclopropane and oxygen are withheld,

the child becomes blue, the pulmonary stenotic murmur becomes shorter, and the pulmonary artery pressure falls. Oxygen diminishes the cyanosis but does not alter the murmur or raise the pulmonary artery pressure. Wood concluded that infundibular contraction can occur, causing an increase in the right to left shunt, and almost total pulmonary ischaemia, leading to syncope and deep cyanosis. This infundibular overaction can be released by cyclopropane, or possibly by other agents which produce rapid anaesthesia or deep narcosis

It is thus apparent that the pulmonary blood flow in the Tetralogy is dependent upon a variable, as well as a fixed, obstruction to right ventricular outflow.

The effect of the right to left shunt upon the pulmonary circulation and respiratory function. As has already been said, poorly oxygenated blood passes directly from the right ventricle into the aorta, and has the double effect of depriving the lungs of blood and producing arterial desaturation The magnitude of the right to left shunt is dictated by the severity of the pulmonary stenosis, the position of the aortic root being usually unimportant

Diffusion of gases across the alveolo-capillary membrane is normal, so that pulmonary venous blood is fully saturated

The central right to left shunt impairs the efficiency of oxygen transport from the lungs to the tissues, however. This impairment occurs in two ways. First, the capacity for oxygen absorption is restricted by the limited pulmonary flow, and second the oxygen tension of arterial blood which is supplied to the tissues is reduced by the admixture of venous blood.

The mechanisms of adaptation to a right to left shunt have been studied by Davison *et al* (1953) The resting oxygen consumption is slightly, but not significantly above the normal range. Assuming a normal resting oxygen consumption, these workers found a highly significant negative correlation between effective pulmonary blood flow, expressed as a percentage of normal, and oxygen capacity Oxygen uptake is maintained by an increase in oxygen absorptive capacity of mixed venous blood. An increase in effective absorptive capacity can be achieved either by a decrease in oxygen saturation of mixed venous blood or by an increase in oxygen capacity resulting from an increase in haemoglobin. Davison *et al.* have shown that both mechanisms operate to maintain resting oxygen uptake in cyanotic congenital heart disease. Increased haemoglobin also helps to maintain tissue oxygen tension at rest when the effective pulmonary flow is less than half the average normal. Davison *et al* also investigated the effect of exercise on four patients with the Tetralogy The arterial venous oxygen saturation decreased on effort, while the oxygen consumption and effective pulmonary blood flow increased in all. The right to left shunt increased in two and fell in two. The respiratory response to exercise was abnormal, the time taken for ventilation to stabilize during a standard exercise test was longer than normal, and this delay was directly proportional to the severity of the arterial desaturation at rest.

Respiratory function at rest has been studied by Shephard (1955) and also by Davison *et al* (1953) Both workers found hyperpnoea at rest a constant feature. This was due to an increase in tidal volume, and was in most cases inefficient as regards oxygen exchange. The chemical composition of the blood indicated a mild compensated hyperventilation, with decreased carbon dioxide content, and alkali reserve, and normal carbon dioxide

tension and pH in arterial blood (Shephard, 1955). The hyperventilation may be the result of a relative hypercapnoea stimulating the respiratory centre, and related to the right to left shunt and reduced pulmonary blood flow. No evidence has been produced to suggest that the respiratory centre is unduly sensitive in these patients. The exact nature of the severe dyspnoea which affects subjects with profound pulmonary oligaemia and a right to left shunt is not fully understood. It is likely to be, at least partly, due to the resting hyperpnoea and increased ventilation and to the fall in oxygen saturation on effort It cannot be ascribed to deficient pulmonary function since the lungs themselves are normal, and pulmonary venous blood fully saturated.

The cause of the attacks of hypercyanosis with dyspnoea and syncope has already been discussed. Closely allied to this syndrome is the phenomenon of squatting, whereby patients obtain some relief from dyspnoea by assuming this position. The incidence of squatting is directly related to the severity of the pulmonary stenosis and the degree of right to left shunt. In extreme cases the subject assumes the squatting position at rest, in less severe cases after effort. The arterial oxygen saturation rises during squatting, perhaps because compression of the aorta increases the resistance to systemic outflow, thus tending to reduce the right to left shunt and enable more blood to reach the lungs. Brotmacher (1957a) has shown that the blood flow to the legs is reduced, and that this results in an increase in cardiac output to the upper half of the body. The consequent reduction in the arterio-venous oxygen difference reduces hypoxia to the respiratory centre. He has also shown that squatting, by impeding the venous return from the legs, reduces the amount of desaturated blood returning to the right side of the heart. This reduced venous return diminishes the right to left shunt and also the tendency for the arterial oxygen saturation to fall with exercise (Brotmacher, 1957b).

Squatting occurs more frequently in the Tetralogy of Fallot than in any other cyanotic lesion.

The magnitude of the right to left shunt is indicated by the level of arterial oxygen saturation which is usually below 85 per cent at rest (normal 93–97 per cent) Secondary polycythaemia occurs in over 80 per cent of such cases. Some cases, as has been mentioned, show little or no clinical cyanosis, and the arterial oxygen saturation is then between 87–95 per cent. The presence of any left to right shunt can be detected at cardiac catheterization by finding a higher oxygen saturation in right ventricular than in right atrial and caval blood Frequently, however, samples from all chambers in the right side of the heart show an equal saturation, but, of course, the arterial oxygen saturation is reduced.

In the absence of a left to right shunt the pulmonary and systemic blood flows may be calculated by the Fick principle from the formulae·

$$\text{Pulmonary flow (l./min.)} = \frac{\text{Oxygen consumption (ml/min)}}{\text{Pulmonary vein minus Pulmonary artery oxygen content (ml./l.)}}$$

$$\text{Systemic flow (l./min.)} = \frac{\text{Oxygen consumption (ml./min.)}}{\text{Systemic arterial minus Right atrial oxygen content (ml./l)}}$$

The assumption is made that pulmonary venous blood is fully (97 per cent) saturated (Wood, 1956).

It will be appreciated that the pulmonary flow is usually less than the systemic because of the right to left shunt, the difference in the equation being that fully saturated pulmonary vein blood is used to calculate pulmonary flow and desaturated systemic arterial blood to calculate the systemic flow. Similar formulae are used to calculate the size of a left to right shunt, when the systemic is less than the pulmonary flow. In the presence of both

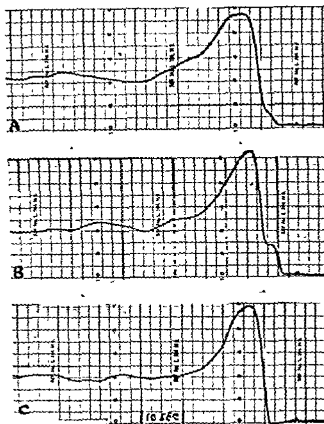


FIG 110 Dye dilution curves recorded from right atrium (*A*), right ventricle (*B*) and pulmonary artery (*C*) The right to left shunt is shown by the premature hump on the upstroke in RA and RV curves, but not in PA There is a small left to right shunt also (Case of Fallot's Tetralogy with minimal cyanosis)

left to right and right to left shunts the overall shunt can be obtained by subtracting the smaller from the larger. This will be discussed later.

The shunts may also be detected by means of dye dilution techniques (Swan and Wood, 1953). Dye such as Evans Blue injected into the right atrium and right ventricle in the Tetralogy reveals the right to left shunt by a premature "hump" on the upstroke of the normal curve, as some of the dye reaches the cuvette or ear oximeter early, having by-passed the lungs. The size of the "hump" is roughly proportional to the size of the shunt, and the appearance time shortened (about 3 sec.) When injected into the pulmonary

tension and pH in arterial blood (Shephard, 1955) The hyperventilation may be the result of a relative hypercapnoea stimulating the respiratory centre, and related to the right to left shunt and reduced pulmonary blood flow. No evidence has been produced to suggest that the respiratory centre is unduly sensitive in these patients. The exact nature of the severe dyspnoea which affects subjects with profound pulmonary oligaemia and a right to left shunt is not fully understood. It is likely to be, at least partly, due to the resting hyperpnoea and increased ventilation and to the fall in oxygen saturation on effort. It cannot be ascribed to deficient pulmonary function since the lungs themselves are normal, and pulmonary venous blood fully saturated.

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The assumption is made that pulmonary venous blood is fully (97 per cent) saturated (Wood, 1956).

covered by the pulmonary artery to the usual extent. An aortic systolic click may be heard if the aorta is very large. Thus in the Tetralogy, the second heart sound is usually described as single and sometimes increased in intensity. The auditory impression of increased loudness is facilitated by the termination of the murmur before the aortic valve closes. Right atrial gallop and pulmonary systolic ejection click, seldom, if ever, occur, and diastolic murmurs are not usually heard even in the presence of a patent ductus arteriosus or large bronchial artery anastomosis (Wood, 1956).

Fig. 111a shows a phonocardiogram from a patient with the Tetralogy. The loud ejection murmur should be contrasted with that of pulmonary hypertension (Chapter 4),

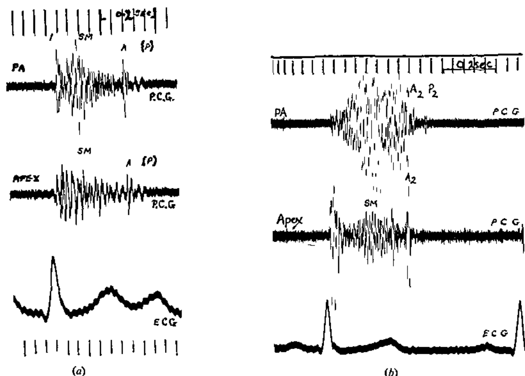


FIG 111 Phonocardiogram (P C G) in (*a*) the Tetralogy of Fallot, and (*b*) pulmonary stenosis with closed ventricular system

SM = systolic murmur　　PA = pulmonary artery area
A = aortic valve closure　　Apex = cardiac apical region
P = pulmonary valve closure

and with that of pulmonary stenosis with closed ventricular septum (Fig. 111b) The pulmonary closure sound is very insignificant, in marked contrast to the large vibration in pulmonary hypertension.

The radiological and angiographic appearances have been described in Chapter 5 and the cardiogram in Chapter 7.

Modifications in the pulmonary circulation resulting from operative treatment. The effects of operations designed to increase the pulmonary blood flow upon the pulmonary

artery, a normal curve results, showing that the right to left shunt is proximal to the pulmonary valve. Fig 110 shows a dye dilution curve from the right ventricle in a patient with the Tetralogy. The premature hump of the right to left shunt is clearly seen. Dye dilution curves made from an injection into the right heart and recorded from an ear oximeter provide a highly sensitive method of detecting and localizing small right to left shunts (Oakley *et al.*, 1960) (Fig. 114).

When a left to right shunt is present in addition, injections from all sites in the right side of the heart show a slow, plateau-like downstroke, due to abnormal recirculation from the shunt. The normal recirculation peak is absent.

Evans Blue (T. 1824) dye has now been largely replaced by Cardio-green, developed by Wood and his colleagues at the Mayo Clinic, and by Coomassie Blue, introduced by Shillingford at the Postgraduate Medical School of London.

New techniques for diagnosing intracardiac shunts using foreign gases have been investigated by workers from the Clinic of Surgery at the National Heart Institute, Bethesda (Braunwald, *et al.*, 1959). Radiokrypton (Kr^{85}) dissolved in saline is injected into a peripheral vein or into the right side of the heart. The gas passes through the pulmonary capillaries into the expired air and is detected by an end-window Geiger-Muller counter at the mouth. Clearance from the lungs is virtually complete, so that levels of Kr^{85} are only slightly above background. However, when a right to left shunt is present, an injection made proximal to the shunt will result in elevated levels in arterial blood.

Angiocardiography also gives a good indication of the position of the aorta and the magnitude of the shunt (Chapter 5), as has been shown by Goodwin *et al* (1953) and Abrams and Kaplan (1956).

The clinical picture of the typical Tetralogy of Fallot. In moderate or severe cases, dyspnoea on exertion is the rule, while squatting and syncope are common. There is obvious central cyanosis, involving tongue and mucous membranes, with polycythaemia, and clubbing of the digits; these are the signs of the right to left shunt. The remaining signs are those of the pulmonary stenosis, modified by the presence of the overriding aorta.

The arterial pulse is normal or small, while the jugular venous pulse is usually normal, but a small dominant "a" wave 3 cm above the sternal angle occurs in a minority (25 per cent) of cases (Wood, 1956). The cardiac impulse is characteristic, being quiet and tapping in nature, reflecting the hypertrophy without dilatation of the right ventricle which is characteristic of the condition. The normal left ventricular thrust is absent. A systolic murmur is present over the right ventricular outflow tract, and is often accompanied by a thrill It is due to the obstruction to right ventricular outflow, and not to the shunt. It begins early in systole, reaches a crescendo in mid-systole, and diminishes in [illegible] ly diminu- [illegible] interrup- [illegible] 1a) The intensity and length of the murmur vary inversely with the pulmonary blood flow, and in patients with a very marked aortic over-ride and large right to left shunt, or with pulmonary atresia, the murmur may be unimpressive in length and intensity

The pulmonary closure sound is frequently inaudible because of the pulmonary stenosis and aortic override Occasionally it may be discerned, occurring late, and of feeble intensity (Fig. 110a). The aortic closure sound is well heard, since the aortic root is not

While pulmonary valvotomy, infundibular resection, or shunt operations may still be required for emergency relief of extremely cyanotic infants, in older children the treatment of choice is now complete correction of the ventricular septal defect and resection of the stenosis under total cardio-pulmonary by-pass (Kirklin *et al.*, 1959). This operation aims at restoring completely the normal haemodynamics, and although it carries some risk because of poor development of the outflow tract in many cases, with improved techniques the procedure is rapidly becoming a satisfactory one especially in patients with little cyanosis. Extensive pulmonary vascular damage of the type described by Rich (1948) may, however, militate against a successful result. Patients who have had previous shunt operations present special problems.

Pulmonary Stenosis with Closed Ventricular Septum

When the foramen ovale is closed, there is no intracardiac shunt, and the effects on the pulmonary circulation are limited to the obstruction to pulmonary blood flow When the foramen ovale is open there is no shunt unless the pulmonary stenosis is extreme, when the pressure in the right atrium exceeds that in the left and forces open the foramen.

The stenosis is valvular in the great majority of cases, but isolated infundibular stenosis occasionally occurs. The main pulmonary trunk is always enlarged when the stenosis is valvular, but the main branches are usually small The peripheral branches, as in the Tetralogy of Fallot, are small, but there is no tendency for thrombosis to occur. Exuberant bronchial artery anastomoses are unusual. Pulmonary blood flow is reduced, and since there is no shunt, the cardiac output is restricted also and dependent upon the severity of the obstruction to the pulmonary artery. As far as is known respiratory function is normal. Pulmonary venous blood is normally saturated, and gas diffusion is normal. It is understandable, therefore, that dyspnoea is not necessarily a prominent feature, and may indeed be only slight in quite severe cases. Symptoms are due mainly to the effects of the low cardiac output. tiredness, fainting on exertion, and sometimes anginal pain The cause of the dyspnoea, when it occurs, is uncertain It can scarcely be chemical, since the arterial saturation is normal and hypercapnoea does not occur. The lungs are not congested, or stiff (the left atrial pressure is normal or low), airway resistance is not increased, and ventilation-perfusion relationships are normal. The arterial oxygen saturation does not fall on effort, unless there is a patent foramen ovale and venous blood shunts into the left atrium, when a small fall may occur. It may be that the muscular effort of breathing is exhausting in the presence of a low cardiac output, and certainly considerable degrees of stenosis may be unassociated with any severe symptoms.

Since the ventricular septum is closed, there is nothing to prevent the systolic right ventricular pressure from rising above the left. The right atrium, in an attempt to assist right ventricular contraction, hypertrophies and a large atrial pressure wave ("a" wave) develops in the jugular venous pulse. In all but mild cases the "a" wave is prominent. In severe cases the right ventricular systolic pressure may reach levels of well over 100 mm. Hg and in extreme cases over 200 mm. Hg. In the latter the right atrial contraction is very powerful, and the "a" wave towers above the "v" (giant "a" wave) It is in such cases that the valve of the foramen ovale if unsealed may be forced open and permit a right to left shunt.

circulation are of some interest. Operations for relief of the Tetralogy are of three main types.

1 "Shunt" operations·
   (*a*) Subclavian-pulmonary artery anastomosis (Blalock-Taussig operation).
   (*b*) Aorto-pulmonary artery anastomosis. (Pott's operation).
2. Closed pulmonary valvotomy by the ventricular route (Brock).
3. Open operation during total cardio-pulmonary by-pass for closure of the defect and pulmonary valvotomy.

The well-known Blalock-Taussig operation is followed by considerable modification in the haemodynamics As a result of the subclavian-pulmonary artery anastomosis the pulmonary blood flow is improved, the cyanosis and clubbing diminish, effort tolerance improves, and squatting is abandoned. A continuous murmur is heard in the region of the shunt, and the arterial pulse may assume a slightly collapsing quality. Cardiac enlargement may occur, but lung vascularity is not usually altered significantly on radiological criteria. The right ventricular pressure is, of course unaltered, as the pulmonary stenosis is not relieved. Occasionally heart failure may occur if the shunt is too great for the left ventricle to sustain. Such failure is thought to be related especially to patients with extreme dextroposition of the aorta (Keith *et al.*, 1958). Following direct aorto-pulmonary anastomosis in older children, the clinical picture may be transformed into that of a large patent ductus, cyanosis being virtually absent. A large collapsing pulse and loud continuous murmur are associated with enlargement of the left ventricle the lungs may appear overfilled on X-ray, and the pulmonary blood flow is substantially increased by the left to right shunt thus created Ross *et al.* (1958) have recently reported disappearance of the anastomotic murmur and increase in cyanosis due to narrowing of small pulmonary arteries. Ferencz (1959) has described rupture of small pulmonary arteries following shunting operations, but it is not known if such damage leads to arterial occlusion later. However, Ferencz and Taussig (1959) have claimed that an anastomosis of moderate size has a beneficial effect upon the pulmonary vascular bed by causing resolution of intravascular thrombi

A technically satisfactory infundibular resection is followed by greater improvement when judged by effort tolerance and disappearance of cyanosis than that obtained from a shunt operation, but half the cases with a striking result are converted into cases of ventricular septal defect, with large left to right shunt and pulmonary plethora. Haemodynamic studies have revealed an isolated left to right shunt, despite the overriding aorta; evidence in support of the thesis that resistance to right ventricular outflow rather than the position of the aorta is the important factor in determining a right to left shunt Wood (1958b) reports that in such cases the pulmonary artery pressure is raised, the right ventricular pressure still equals that of the left, and the calculated pulmonary resistance is normal. The Eisenmenger reaction, with balanced pulmonary and systemic resistances and shunts does not apparently occur (Wood, 1956). The long-term results are better after adequate direct operations than after the anastomic procedures, for in many cases the anastomosis closes (Campbell, 1958a).

All cases treated either by a shunt or by direct operation on the pulmonary valve show relief of dyspnoea proportional to the increase in pulmonary blood flow, indicating the importance of diminished pulmonary blood flow in the production of dyspnoea.

... and the augmented "a" wave, together with the more ... radiological appearances in the latter ... 1957; Campbell, 1958b).

Fig. 111b shows distinctive phono... tenosis

The radiological and cardiographic appearances are ... Chapters 5 and 7 respectively.

The pressure pulses in pulmonary artery and right ventricle are those of valvular stenosis in 80–90 per cent of cases, and infundibular stenosis in the remainder.

The Tetralogy of Fallot and lone pulmonary stenosis typify the abnormalities of the pulmonary circulation which occur as a result of obstruction to right ventricular outflow, with and without a right to left shunt respectively. Cyanotic conditions which may also be associated with reduced blood flow to the lungs, such as persistent truncus arteriosus, ... tricuspid atresia, will not be discussed, except in so far as they are associated with ... the lungs, which will be mentioned below. Conditions such as ... ricuspid valve (Engle *et al.*, 1950) have no especial pulmonary circulatory ... which differs from that in lone pulmonary stenosis, and therefore also will not be described.

Unilateral pulmonary stenosis. Multiple peripheral pulmonary stenoses. An unusual type of pulmonary stenosis has been described in which obstruction occurs distal to the pulmonary valve in one or more large branches. The obstruction probably takes the form of a congenital band or stricture. Cardiac catheterization shows a pressure gradient between peripheral and main pulmonary arteries, and cardiac defects may also be present. Hypertension exists in the main pulmonary arteries proximal to the stricture and a continuous murmur has been reported at the base of the heart (Gunning 1957; Smith, 1958).

Effects of Surgical Treatment in Lone Pulmonary Stenosis

Effective pulmonary valvotomy reduces the gradient across the pulmonary valve, improves pulmonary blood flow and vascularity, and reduces the size of the heart. The cardiogram also sh... in younger subjects (Campbell, 1959). ... 959) may result in a persistent gradient ... The infundibulum may thus require resection also, which is best performed under cardio-pulmonary by-pass (McGoon and Kirklin, 1958).

2. BRONCHIAL ARTERY "PULMONARY" CIRCULATION

Enlarged bronchial arteries are found in severe cases of the Tetralogy of Fallot, they are seen predominantly in cases of pulmonary atresia, tricuspid atresia, and persistent truncus arteriosus, and have also been found in a case of extra-pulmonary venous stenosis (Bernstein *et al.*, 1959). Taussig (1947) discusses the possible alternative routes by which blood may reach the lungs in cases of complete pulmonary atresia with closed ductus arteriosus. Other vessels of the collateral circulation to the lungs are the anterior and posterior mediastinal arteries, oesophageal artery branches, pericardial arteries and even

The arterial pulse is normal or small. The cardiac impulse is diffuse and tapping, indicating right ventricular hypertrophy, which only causes a sternal lift in severe cases

There is a systolic thrill over the pulmonary artery area, and a long loud ejection murmur which extends over the aortic component of the second heart sound. The pulmonary component is soft and delayed, but can usually be heard (Fig. 110b). The auscultatory phenomena therefore vary in important ways from the Tetralogy, in which, because

TABLE 9

DIFFERENTIAL DIAGNOSIS

Tetralogy of Fallot	*Severe lone pulmonary stenosis with patent foramen ovale and closed ventricular septum*
1. Cyanosis early and more severe	Cyanosis delayed· less increase on effort
2. Chest deformity not infrequent	No chest deformity
3 Jugular venous "a" wave small or moderate	"Giant" "a" wave
4. Systolic murmur terminates early, and may be soft (Fig. 111a)	Murmur very long and full length (Fig *111b*)
5. Single (aortic) loud second heart sound Pulmonary closure usually inaudible	Delayed soft pulmonary closure sound
Radiology	
6. *Heart not greatly enlarged* Main pulmonary artery small or moderately enlarged Right atrium not enlarged Right-sided aortic arch in 25 per cent	*Heart may be greatly enlarged* Main pulmonary artery usually dilated Right atrium prominent
Cardiogram	
7. Moderate or severe right ventricular hypertrophy	Very severe right ventricular hypertrophy with inverted right praecordial T waves
Cardiac catheterization	
8. Pressures equal in systole in both ventricles Aorta often entered from right ventricle	Right ventricular pressures higher than left ventricle in systole Aorta not entered from right ventricle
Dye dilution studies	
9. Right to left shunt from right ventricle	Right to left shunt from right atrium
Angiocardiography	
10. Aorta fills before, or simultaneously with, pulmonary artery	Left atrium fills from right atrium early, and aorta fills from left ventricle

much of the right ventricular blood is diverted into the aorta, the murmur tends to be shorter, aortic valve closure is louder, and pulmonary closure frequently inaudible A further difference is that a right atrial (fourth) heart sound is often heard in severe lone pulmonary stenosis but not in the Tetralogy.

The decision whether the ventricular septum is patent or not in cases of pulmonary stenosis may be difficult. The problem arises when cyanosis is due either to a right to left shunt across the ventricular septum as in the Tetralogy, or through a patent foramen ovale in severe cases of lone pulmonary stenosis when the ventricular septum is closed.

ventricular septal defect and pulmonary stenosis The bronchial arteries were enlarged, and direct widespread precapillary anastomoses with the pulmonary arteries by vasa-vasorum were demonstrated.

An exuberant bronchial circulation was well shown in a child of 12 years who was grossly cyanosed, and severely dyspnoeic. Angiocardiography confirmed the clinical diagnosis of both pulmonary and tricuspid atresia, and showed a right-sided systemic outflow tract, from which arose a tortuous artery at the level of the right hilum (Fig. 112a).



FIG 112b Post-mortem angiogram of the same patient as fig 112a showing extensive bronchial circulation The lungs have been injected through the aorta with barium gelatin mixture. The large bronchial arteries form the sole blood supply to the lungs (Same patient as fig 71 chap 6)

The patient succumbed to repeated profuse haemoptyses some years later, and post-mortem confirmed the diagnosis. The pulmonary artery was totally atretic, the lungs being supplied entirely by hypertrophied bronchial arteries, which can be seen in the post-mortem angiogram (Fig. 112b). The cause of the haemoptyses was considered to be rupture of large varicose bronchopulmonary artery anastomoses.

Detection of bronchial arteries is of some clinical importance, since it suggests that the pulmonary arteries are rudimentary, or even absent, and that the usual forms of surgical treatment may therefore not be feasible. For such cases, with absent or trivial pulmonary arteries, Barrett and Daley (1949) evolved an operation consisting of dusting asbestos in

anomalous branches from the coronary arteries. Although enlarged bronchial arteries can easily be seen, and their origin traced to the aorta, the exact way in which they anastomose with the pulmonary circulation is nearly impossible to determine (Taussig, 1947) Little is known of the haemodynamics in the pulmonary circulation in such cases, but recently clinical and pathological studies of bronchial artery syndromes have increased knowledge of the collateral circulation to the lung. The radiological appearances of bronchial arteries are described in Chapter 5.

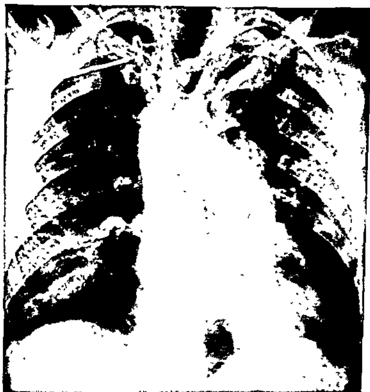


FIG 112a Angiocardiogram in tricuspid and pulmonary atresia. The large bronchial artery can be seen arising from the "aorta" in the region of the right hilum

Clinically, bronchial circulation to the lungs may be suspected in an intensely cyanosed subject in whom the absence of a pulmonary stenotic murmur and pulmonary closure sound suggests pulmonary atresia. A faint high-pitched continuous murmur arising from the bronchopulmonary arterial anastomoses can be heard over the chest wall, or down the sternal edge. In general, the poorer the pulmonary arteries, the greater the cyanosis and dyspnoea, and the greater the development of the bronchial arteries. Indeed, when pulmonary atresia is present, and the ductus arteriosus closed, life is dependent upon the pulmonary circulation provided by bronchial and other anastomotic arteries.

Cudkowicz and Armstrong (1952) studied the bronchial circulation at necropsy by histological and injection techniques in a case of transposition of the great vessels with

any rise in pressure in the pulmonary artery. The blood passing through the pulmonary veins is fully saturated. The occasional occurrence of slight arterial desaturation in patients with a left to right shunt and normal pulmonary vascular resistance has been attributed to failure of full oxygenation owing to such rapid passage of blood through the capillaries that insufficient time is available for full oxygen saturation to occur. This is probably never the case, alternative explanations being available, which will be discussed later. In spite of the increased pulmonary venous and left atrial inflow, severe pulmonary venous hypertension does not occur, unless left ventricular failure is present. If so, the increase in left ventricular filling pressure which results, produces an increase in left atrial pressure. But the high levels of pulmonary venous pressure found in mitral disease are seldom if ever seen.

When pulmonary blood flow is torrential, however, pulmonary arterial hypertension occurs, the vascular resistance rising as the pulmonary vessels reach their limit of elastic distensibility. This results in hyperdynamic hypertension, which has previously been discussed in Chapter 4. In such cases, the additional factor of vasoconstriction comes into play. When the pulmonary blood flow exceeds approximately three times normal (15–20 litres/min.), further increases in flow are accompanied by an increase in pressure. In some cases, however, the pulmonary pressure is appreciably raised at flow rates below these figures, indicating that the resistance is elevated This elevation is considered to be vasoconstrictive rather than organic, because abrupt closure of the shunt with reduction in pulmonary blood flow can be accompanied by a fall of pressure to within the normal range (Fig. 5 in Chapter 4) The presence of pulmonary vasoconstriction has also been demonstrated by the effects of oxygen and acetylocholine on the pulmonary circulation (see Chapter 4), while 5-Hydroxytryptamine has also been shown to produce pulmonary vasoconstriction in the dog (Rudolph and Paul, 1957).

Pulmonary vascular resistance is estimated by the formulae shown in Chapter 4, p. 11.

Wood (1956) reports that "appreciable reactive pulmonary vasoconstriction occurred in 25 per cent of 100 critical cases of atrial septal defect, and in 68 per cent of 100 critical cases of ventricular septal defect or patent ductus". He defines as critical a defect of sufficient size to cause a pulmonary blood flow at least three times the systemic flow with a normal resistance. In his 93 cases which developed the vasoconstrictive reaction, the pulmonary resistance was considerable in the minority and extreme in the majority (10–30 units, average 17, normal 0–2) He believes that the vasoconstriction occurs at birth in the majority of patients who develop it. It is not known why it occurs in some cases but not in others. Certainly high pulmonary flows can exist for many years without appreciable vasoconstriction, as was shown by a patient with patent ductus arteriosus, who at the age of 49, was found to have a pulmonary blood flow of 25 litres/min. and a pulmonary arteriolar resistance of under one unit (Fairley and Goodwin, 1959)

Chronic hypoxia, which causes vasoconstriction under other circumstances (Chapters 4 and 8), does not occur in this group of disorders. Neither does appreciable pulmonary venous hypertension occur, although the pulmonary capillary venous pressure is often slightly raised in large ventricular septal defects. Wood's (1956) hypothesis that vasoconstriction develops under the stimulus of pulmonary hypertension itself is an attractive one.

When extreme levels of pulmonary vascular resistance have developed, the left to

the pleural cavity, causing extensive adhesion formation, and inviting collateral circulation to develop through the adhesions.

3. LESIONS ASSOCIATED WITH AN INCREASED PULMONARY BLOOD FLOW

This group consists of patients with a *communication which permits blood to shunt* from the left to the right side of the heart. The normal pulmonary blood flow from the right ventricle is augmented by blood which has already been through the lungs. The shunt may be at caval, atrial, ventricular, or pulmonary artery level, and may be classified as follows.

1. *At caval level:*

   Anomalous pulmonary venous connection (usually associated with atrial septal defect).

2. *At atrial level:*

   (*a*) Atrial septal defect.
   (*b*) Partial anomalous pulmonary venous drainage or connection.
   (*c*) Total anomalous pulmonary venous connection.

(Note that a patent foramen ovale is not associated with a left to right shunt.)

3. *At ventricular level:*

   Ventricular septal defect (with or without transposition of pulmonary artery and aorta).
   Single ventricle (without pulmonary atresia).

4. *At pulmonary artery level:*

   (*a*) Patent ductus arteriosus.
   (*b*) Aorto-pulmonary defect.

Shunts at any level may be complicated by transposition or tricuspid atresia. A complete list of malformations will not be attempted, and only those which illustrate specific alterations in the pulmonary circulation will be considered.

Haemodynamics and pulmonary circulation in left to right shunts. Wherever the site of the shunt, the circulatory dynamics have certain features in common. In every case the pulmonary blood flow is increased, the size of the shunt often being proportional to the size of the defect provided that severe obstruction to the pulmonary vascular bed has not restricted the shunt. The right ventricle has extra work to do in pumping the normal systemic venous return, plus the blood shunted from the left side of the heart, into the lungs This load is greatest in atrial septal defect and least in patent ductus. The ventricle consequently dilates and undergoes hypertrophy. The increased blood flow to the lungs causes dilatation and excessive pulsation of the main and medium-sized pulmonary arteries, most marked in cases of atrial septal defect. The pulmonary blood flow, when only moderately increased, can be accommodated in the distensible pulmonary vessels without

Therefore:

Left to right shunt = *Total pulmonary artery flow* minus *effective pulmonary artery flow*.

Right to left shunt = *Systemic flow* minus *effective pulmonary artery flow*.

It follows that when a right to left shunt is absent, systemic flow is equal to the effective pulmonary artery flow. "Mixed venous" refers to blood sampled from the cardiac chamber proximal to the level of the shunt: in atrial shunts from the cavae; in ventricular shunts from the right atrium, and in aorto-pulmonary shunt from the right ventricle. In cases with bi-directional shunts, the overall shunt is obtained by subtracting the smaller shunt from the larger. The pulmonary-to-systemic flow ratio may be determined by the formula:

$$\frac{\text{Pulmonary flow}}{\text{Systemic flow}} = \frac{O_2 \text{ content of arterial blood } minus \;\; O_2 \text{ content of mixed venous blood}}{O_2 \text{ content of pulmonary vein blood } minus \;\; O_2 \text{ content of pulmonary artery blood}}$$

Dye dilution techniques also may be used to detect the presence of a left to right shunt, but do not localize the site unless injected into the left side of the heart. An injection into the left side of the heart distal to the shunt will give a normal curve, but one made at the site of the defect will show a left to right shunt pattern (Swan and Wood, 1957). The characteristics of a left to right shunt are a normal right-sided appearance time (about six seconds, depending upon the site of the injection, a sharp build-up, but a prolonged fall off, punctuated by a number of small humps on its early portion, representing early re-circulation due to the shunt). The magnitude of the shunt may very roughly be gauged by the f [illegible] spread of the curve and the slowness of the fall-off ("skewing"). Injections [illegible] heart and recorded by an ear oximeter do not localize the [illegible] is also present. But dye curves made [illegible] using [illegible] le value as a screening test for the [illegible] the technique [illegible] in be used to supplement the data [illegible] *et al.*, 1960). If dye is injected into the right heart and sampled [illegible] oximal chamber using a cuvette densitometer, the shunt can be localized, for the [illegible] corded at the site of the shunt will have an earlier appearance time than that recorded from a systemic artery. Calculations based on the upstroke of the curves have been used to assess the magnitude of the shunt (Russell *et al.*, 1958). When an additional right to left shunt is present, the site of the right to left shunt can be localized with precision, for the characteristic dye curve will not be obtained from an injection into a chamber distal to the shunt, provided valvular incompetence is absent (Korner and Shillingford, 1955). A simpler method for localizing left-to-right shunts at catheterization of the right heart has been described by Braunwald *et al.* (1959). Dye is injected into a vein and sampled from the right heart. Sampling distal to, but not proximal to, the shunt will reveal its site by a prolonged down slope of the curve. Fig. 114 shows in diagrammatic form, dye curves in the normal, in left to right shunts, and bi-directional shunts obtained by injecting dye into the heart and using the ear oximeter.

Techniques with foreign gases may also be used to detect left to right shunts (Braunwald *et al.*, 1959). During the inhalation of an inert foreign gas such as Nitrous oxide, the

right shunt becomes reduced or negligible, and a right to left (reversed) shunt may occur This constitutes the Eisenmenger reaction or syndrome which will be fully discussed later.

The pulmonary vascular pattern in congenital heart disease is strikingly different from that in mitral disease (Doyle *et al.*, 1957) (Chapters 5, 6 and 8). Narrowing of small pulmor
evenly (
small a
hypertrophy, and later by occlusion in some cases. The initial constriction could well be precipitated, as Wood has suggested, by pressure. Fig. 113 shows diagrammatically the distribution of the vascular pattern, which should be contrasted with that in mitral stenosis (Chapter 8).

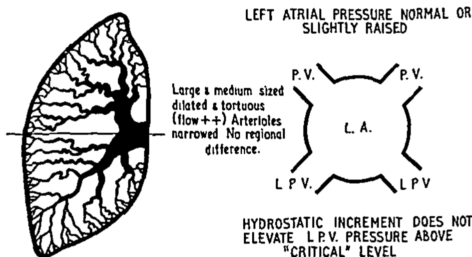


FIG. 113 Diagram of pulmonary vascular pattern in congenital heart disease.
L P V = pulmonary vein to lower zones
P V = pulmonary vein to upper zones
L.A. = left atrium

The estimation of left to right shunts. The magnitude of shunts can be roughly assessed by the use of the Fick principle and the formulae of Friedlich *et al.* (1950)

$$\text{Systemic blood flow (ml. per min.)} = \frac{O_2 \text{ uptake ml. per min.} \times 100}{O_2 \text{ content arterial blood } \textit{minus } O_2 \text{ content mixed venous blood (Vols \%)}}$$

$$\text{Total pulmonary artery flow (ml. per min.)} = \frac{O_2 \text{ uptake} \times 100}{O_2 \text{ content pulmonary vein blood } \textit{minus } O_2 \text{ content pulmonary artery blood (Vols. \%)}}$$

$$\text{Effective pulmonary artery flow} = \frac{O_2 \text{ uptake} \times 100}{O_2 \text{ content pulmonary vein blood } \textit{minus } O_2 \text{ content mixed venus blood (Vols. \%)}}$$

Therefore:

Left to right shunt = *Total pulmonary artery flow* minus *effective pulmonary artery flow.*

Right to left shunt = *Systemic flow* minus *effective pulmonary artery flow.*

It follows that when a right to left shunt is absent, systemic flow is equal to the effective pulmonary artery flow. "Mixed venous" refers to blood sampled from the cardiac chamber proximal to the level of the shunt: in atrial shunts from the cavae; in ventricular shunts from the right atrium, and in aorto-pulmonary shunt from the right ventricle. In cases with bi-directional shunts, the overall shunt is obtained by subtracting the smaller shunt from the larger. The pulmonary-to-systemic flow ratio may be determined by the formula:

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Techniques with foreign gases may also be used to detect left to right shunts (Braunwald *et al*, 1959) During the inhalation of an inert foreign gas such as Nitrous oxide, the

concentration in the left side of the heart or systemic artery rises sharply and then levels off. The concentration in the venous system rises more slowly, so that in the absence of shunts blood from the right heart contains a small but constant amount (about 10 per cent) of the gas present in arterial blood. When there is a left to right shunt, however, the concentration will be higher than normal in the right heart blood, and the presence of a shunt can be gauged from the ratio of gas concentration of right heart blood to arterial blood. The magnitude of the shunt can be calculated from a knowledge of the gas content of venous blood, shunted blood and pulmonary arterial blood. The concentration of gas in the venous blood proximal to the shunt is around six per cent of the arterial level, while the

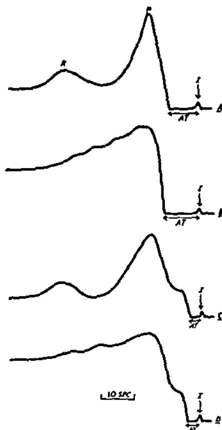


FIG 114 Diagrams of dye dilution curves in intracardiac shunts.
(*A*) Normal
(*B*) Large left to right shunt.
(*C*) Right to left shunt.
(*D*) Bidirectional shunt.
I = injection
AT = appearance time
P = peak
R = recirculation

nitrous oxide content of shunted blood is the same as that of arterial blood. The pulmonary-to-systemic flow ratio may be calculated from the formula:

$$\frac{\text{Pulmonary flow}}{\text{Systemic flow}} = \frac{100\% - \text{R.A.}\%}{100\% - \text{P.A.}\%}$$

where P.A.% = concentration of gas in pulmonary artery blood
R.A.% = concentration of gas in right atrial blood
100% = concentration of gas in systemic arterial blood (Sanders *et al.*, 1959)

Kr^{85} may be used instead of nitrous oxide for easier and faster analysis (Sanders, 1958)

Pulmonary function in patients with left to right shunts. Pulmonary function is usually within normal limits. There is no impairment of gas exchange, while bellows function, mixing, and airways resistance are normal. However, respiratory infections and segmental atelectasis tend to occur. The lungs might be expected to be unduly stiff and inelastic, especially when heart failure has occurred, as may happen in children with large ventricular septal defects. McNeill *et al.* (1958) have studied three patients with "pulmonary congestion". One had congestive heart failure of unknown cause, one had mitral valve disease, and the third an atrial septal defect with pulmonary flow of thrice the systemic. In all three patients the pulmonary capillary blood volume was increased and in the patients with atrial septal defect and mitral disease the true diffusing capacity of the pulmonary membrane was normal. Fleming (1959), using bronchospirometry, found that the oxygen uptake of the right lung was greater than that of the left in 25 patients with atrial septal defect, possibly due to preferential draining of the blood from the right lung across the defect, and to the enlargement of the heart compressing the left lung.

Atrial Septal Defect

Defects may be single or multiple, large or small, and are of three main types. The persistent ostium primum type overlies the tricuspid valve orifice, the lower margin being formed by the ventricular septum, and the atrio-ventricular valves, which may be malformed. A common atrio-ventricular canal may be present. There is often a left to right shunt at ventricular as well as atrial level. The much commoner ostium secundum, or fossa ovalis defect, lies higher in the septum, but may extend down to the inferior cava, lying astride the caval orifice, which may empty partly into the left atrium if there is a large Eustachian valve. The third type lies above the fossa ovalis, just below the superior vena cava (Bedford *et al.*, 1957). With this type of defect, upper pulmonary veins on the right side may drain into the right atrium.

Haemodynamics and pulmonary circulation. When the left to right shunt is small, the pressure is greater in the left atrium than in the right, but only by a few millimetres of mercury. When the shunt is large, the pressures are equal, blood passing from the left to the right atrium by virtue of the greater distensibility of the right ventricle than the left in the presence of equal filling pressures. The stroke output of the right ventricle is increased by the left to right shunt, and the right atrium, ventricle and pulmonary artery dilate The main pulmonary arteries are usually massive when the atrial septal defect is large, strikingly more so than in other types of left to right shunt. The left atrial shunt deprives the left ventricle of blood, so that its stroke output is reduced. The left ventricle therefore remains small, as does the aorta. The combination of large pulsating pulmonary arteries, large right atrium and ventricle, with small aorta, is very characteristic of atrial septal defect (Chapter 4) Progressive dilatation of the right ventricle leads to a rise in right atrial pressure, and the shunt may reverse, so that a bi-directional shunt then exists. Usually, however, the left atrial pressure rises also, so that shunt reversal is prevented. The exact reason for this is not known It has been attributed to bulging of the hypertrophied ventricular septum into the left ventricle, obstructing inflow (Wood, 1956). There is no doubt that the right atrial pressure mirrors the left, so that the latter can be assessed by measuring the jugular venous pressure. If left ventricular failure occurs as a result of

associated mitral valve incompetence, for example, the rise in left atrial pressure will transmitted to the right atrium, and the jugular pressure will rise (Dexter, 1956). Tricusp insufficiency is common in late cases of atrial septal defect and reflects stretching of t tricuspid valve ring and right ventricular failure, and may be accentuated by the onset atrial fibrillation.

Fleming (1959) has shown that the right lung carries a greater blood flow than t left, as measured by oxygen consumption during bronchospirometry Central cyano is absent in most cases but arterial desaturation may occur for five reasons·

Frequent· (1) Streaming of inferior vena caval blood across a sinus venosus defec Desaturation is slight, and the pulmonary resistance normal: there is no "shu reversal"

Less common: (2) The pulmonary vascular resistance may be greatly increased, wi increase in pulmonary, right ventricular and right atrial pressures leading to shu reversal (Eisenmenger reaction).

(3) Severe organic pulmonary stenosis may increase right ventricular pressu and lead to shunt reversal

(4) A small right to left shunt may result from right ventricular failure

(5) One of the cavae may enter the left atrium

Cardiac catheterization demonstrates normal pulmonary artery and right ventricula pressures in many cases. When the pulmonary blood flow is torrential, there may be hype dynamic or vasoconstrictive hypertension. In many cases a pressure gradient is presen across the pulmonary valve, but organic obstruction to the right ventricular outflow trac is not necessarily present. The cause for this is not known. It is not merely due to ver high flow, since there is no direct correlation between flow and gradient (McDonald 1958) It may be due to "relative" stenosis of the valve ring, which has not dilated in sympathy with the ventricle and pulmonary artery, or to an artefact (Chapter 2). It has been suggested by Harris (1955) that the form of the right ventricular pressure pulse may indicate whether the gradient is due to true or false obstruction. When the upstroke is smooth and unbroken to its peak, this suggests valvular stenosis, but when the upstroke changes slope near the peak, as in the normal pulse, the obstruction may be infundibular or artefactual This difference has yet to be confirmed as a useful differential diagnostic pointer

The presence of sharp negative deflections (venturi effects) in systole in the last few pulses from the pulmonary artery before the catheter passes through the valve into the right ventricle suggests true valvular stenosis.

Dye dilution curves demonstrate the left to right shunt from all right heart chambers Selective injections from inferior and superior cavae may show a small right to left shunt, due to streaming from the inferior cava, through a fossa ovalis defect. Selective streaming from superior vena cava or inferior vena cava may help to predict the site of the defect (Swan *et al.*, 1954); (Oakley *et al.*, 1960) (Fig. 115). Lee and Gimlette (1957) have demonstrated a fall in arterial oxygen saturation after the Valsalva manœuvre, due to temporary shunt reversal when the obstructed venous return enters the right atrium.

Pulmonary hypertension in atrial septal defect. In 75 to 80 per cent of cases this is hyperdynamic or vasoconstrictive; obstructive hypertension occurs only in the minority.

Indeed many patients have a normal pulmonary arterial pressure, and even in those with some elevation, the resistance is normal. Edwards (1957) states that the pulmonary vascular tree has the characteristics of a low pressure system, the arterioles having thin walls and wide lumina, and are indistinguishable from the normal. However, tortuosity was found in post-mortem angiograms in our series (Doyle *et al*, 1957) (Chapter 6), and indicates a high flow.

Obstructive pulmonary hypertension tends to develop as the patient reaches adult life and may become extreme in the third or fourth decades, when shunt reversal may

A

B 10 sec

Fig [illegible]

both curves.

occur. Patients then become severely breathless and disabled. Examination of the pulmonary vascular tree reveals tortuosity of large and medium arteries, and obstruction to arterioles. The small muscular arteries show hypertrophy in proportion to the degree of hypertension. Focal occlusive lesions with fibrosis of the intima are seen in small arteries and arterioles. Distal to these lesions, the arteriole widens out. Some arterioles have a thin, and some a thick, media in association with intimal thickening and occlusive changes. Perhaps as Edwards (1957) suggests, those with thin media develop intimal lesions before significant elevation of pressure, and therefore medial thickening, occurs. It is virtually certain that medial hypertrophy is at least in part a consequence of hypertension, and that a vicious circle of hypertension, medial hypertrophy, and further hypertension occurs

This is common to all forms of pulmonary hypertension (see Chapter 4) Many of the small vessels are patent, dilatated and devoid of muscle layers. Presumably these vessels dilate to accommodate the flow which cannot pass through the obstructed vessels, the absence of muscle preventing the active vasoconstriction which occurs in other arteries and leads to hypertension and medial hypertrophy. Evans (1951), and Evans and Short (1958) have described intimal proliferation, endarteritis fibrosa, and aplasia of the media in the muscular arteries in atrial septal defects. They claimed that these lesions differed in no way from those found in other forms of severe pulmonary hypertension. They concluded that there was an inherent predisposition to arterial obstruction which led to pulmonary hypertension, but recent views do not support this suggestion.

In atrial septal defect the tendency for severe pulmonary hypertension to manifest itself in adult life, has already been mentioned. The occlusive changes which develop in the small pulmonary arteries are often associated with thrombosis, which may be secondary to necrotizing arterial lesions. Thrombosis in large or main pulmonary arterial branches is also well recognized in atrial septal defect (Canada *et al.*, 1953; Bedford *et al*, 1957) and such large thrombi may arise secondarily to thrombosis in the small branches, or give rise to emboli into the small branches. The reasons for the delayed onset of severe pulmonary hypertension and increased vascular resistance are not fully understood. Perhaps as Dexter (1959) suggests, the high flow and low pressure takes many years to produce pulmonary vascular disease. Possibly right ventricular failure leads to stagnation of pulmonary flow which predisposes to thrombosis.

When pulmonary hypertension becomes extreme, the left to right shunt is reduced as the right to left shunt builds up. Some cases may have solely a right to left shunt, and some virtually no shunt in either direction. Usually, however, a small bi-directional shunt is found. Where this complication has occurred the patient enters the category of the Eisenmenger syndrome, which will be discussed later.

The association of mitral stenosis with atrial septal defect (Lutembacher syndrome) was at one time thought to be common, for early reports stressed its frequency at autopsy. However, recent studies during life suggest that it is a rare disorder (Bedford *et al.*, 1957), although Espino-Vela (1959) has collected twelve recent cases with autopsy proof

The effect of mitral obstruction is to increase the left to right shunt and prevent reversal occurring. The left atrial and jugular venous pressures are therefore raised, and both atria are enlarged. An apical mid diastolic murmur, decreasing on inspiration is present The pulmonary vessels may be expected to show changes of pulmonary venous hypertension and high pulmonary blood flow and the pulmonary vascular pattern of mitral stenosis is likely.

A dogmatic diagnosis is difficult to make in life unless there is persistent elevation of the jugular venous pressure, the left atrial pulse is characteristic of mitral obstruction, there is a diastolic gradient between left atrium and ventricle, calcification of the mitral valve is seen on X-ray, or the mitral valve is found to be stenosed at thoracotomy.

The clinical picture of atrial septal defect. The uncomplicated large ostium secundum defect is characteristic. The patient commonly shows some features of Marfan's syndrome, notably long thin fingers and limbs, and a high arched palate. The arterial pulse is small, or normal in volume, and the jugular venous pulse shows a predominant "v" wave, the "a" wave being normal. The cardiac impulse reflects a dilated and hyper-

dynamic right ventricle, and is diffuse in type, lifting the lower end of the sternum. Auscultation reveals a widely split second heart sound, the pulmonary component failing to widen with inspiration, either because the right ventricle is unable to deal with any further inflow, or because of complete right bundle branch block. An ejection systolic murmur due to excessive pulmonary flow, is commonly heard. A most important sign is the mid-diastolic or presystolic murmur which is accentuated on inspiration and heard over the tricuspid area, and attributed to torrential tricuspid valve flow. The intensity of the murmur is sometimes a clinical guide to the magnitude of the left to right shunt (Fig. 116). A similar murmur, of course, is heard in organic tricuspid valve stenosis.

A suspicion of cyanosis may be present, but clubbing is absent in the uncomplicated defect. The minimal cyanosis is usually due to streaming of venous blood from inferior vena cava to left atrium (Swan *et al.*, 1954).







FIG. 116 Phonocardiogram (P C G) in atrial septal defect·
1 = 1st heart sound
2 = 2nd heart sound
A = aortic valve closure
P = pulmonary valve closure
SM = systolic murmur
MDM = Tricuspid mid-diastolic murmur, conducted to apex, but beat heard in tricuspid area
HF = high frequency
Apex = cardiac apical pulsation

Symptoms are usually slight or absent; tiredness being a particular feature in large defects; it is presumably due to the low cardiac output. Haemoptysis and frequent respiratory infections may occur.

The radiological and cardiographic appearances will be described in the appropriate chapters.

When moderate pulmonary hypertension is present, the pulmonary closure sound is accentuated, and the ejection murmur loud and sometimes accompanied by a thrill.

The picture of extreme pulmonary hypertension will be discussed under the Eisenmenger syndrome

In advanced cases in older subjects, congestive heart failure and tricuspid incompetence may occur. Cyanosis (partly peripheral) is usually present, and slight clubbing may occur. The venous pressure is appreciably raised, with systolic pulsation due to tricuspid incompetence. Atrial fibrillation is not uncommon at this stage, and when this is

present, the venous pulse shows a single systolic pulsation with sharp "y" descent. The heart is greatly enlarged, and there is usually a pansystolic murmur increasing on inspiration at the tricuspid area, due to the tricuspid incompetence.

When true pulmonary stenosis is present, the systolic murmur over the pulmonary area is louder and longer, and is usually accompanied by a thrill, while the pulmonary closure sound is unduly soft and may be greatly delayed. In severe cases the shunt may be reversed, when the tricuspid flow murmur disappears and cyanosis and clubbing appear. Then the "a" wave in the jugular venous pulse becomes augmented. It must be emphasized, however, that pulmonary stenosis of moderate severity is compatible with persistence of a left to right shunt in atrial septal defect.

Anomalous Pulmonary Venous Drainage or Connection

Partial anomalous drainage. Abnormalities of pulmonary venous drainage are not uncommon in association with atrial septal defect (11 per cent in Bedford *et al*'s series, 1957), but they rarely occur in its absence. Abnormal drainage may be distinguished from abnormal connection, the former implying flow of pulmonary venous blood into the right atrium without the vein or veins necessarily entering that chamber. Anomalous venous connection implies that the pulmonary vein is unequivocally connected to the wall of the right atrium or to one of the caval veins.

One or more pulmonary veins may drain into the right atrium or superior vena cava. This is particularly common in high sinus venosus defects, and in large fossa ovalis defects with rudimentary or absent posterior septal rim, so that the right pulmonary veins communicate with both atria (Bedford *et al.*, 1957). The latter type illustrates the difference between anomalous drainage and anomalous connection. The presence of anomalous pulmonary venous drainage, of course, contributes to the left to right shunt caused by the atrial defect.

Anomalous pulmonary veins may be of surgical importance, especially in the high superior caval type of defect (Swan *et al.*, 1957). Diagnosis before operation can usually be made at cardiac catheterization, when the catheter may enter the vein via the right atrium or superior vena cava. However, misinterpretation can occur, for the catheter may pass into the vein after traversing the left atrium across the septal defect and yet appear to have entered the vein directly from the right atrium. Dye dilution curves can give a precise answer when there is a right to left shunt from the inferior cava, for an injection into a lower lobe anomalous vein gives an appearance time identical with that from an injection in the inferior cava or lower right atrium, with a small right to left shunt, which is absent if the vein enters the left atrium in the normal way (Oakley *et al.*, 1960) (Fig. 117). Injections into each main pulmonary artery can detect the presence of anomalous veins draining one lung, when the appearance time from the pulmonary artery of this lung will be longer than from the opposite pulmonary artery from which dye will pass via the normal veins into the left atrium (Swan *et al.*, 1953)

Partial anomalous venous drainage without atrial defect is a rare anomaly, but may clinically exactly counterfeit an atrial septal defect. A fall in arterial oxygen saturation on effort or on performing the Valsalva manœuvre may be detected by oximetry, and reveal the presence of a right to left atrial shunt under stress, while selective injections of dye

into left atrium and ventricle respectively will show a longer appearance time and left to right shunt from the former, but not from the latter if there is an atrial defect.

The passage of the catheter from right to left atrium does not, of course, establish the presence of an atrial septal defect with certainty, since a patent foramen ovale will permit

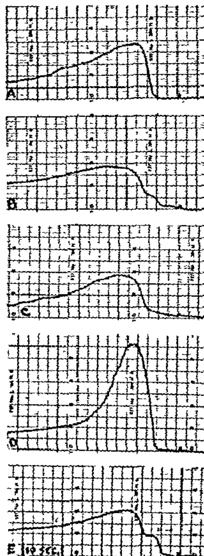


FIG. 117 Dye dilution curves in atrial septal defect with right to left shunt from *inferior* vena cava (IVC) and anomalous pulmonary vein entering the lower portion of the right atrium
(*A*) From SVC
(*B*) From IVC
(*C*) From right atrium
(*D*) From left atrium
(*E*) From anomalous pulmonary vein
The right to left shunt can be seen in (*B*), (*C*) and (*E*) proving that the vein enters the region of the inferior vena cava. A short appearance time can be seen in the left atrial injection

this to occur. An appreciable pressure gradient between the atria excludes a large atrial septal defect but not a small one.

Total anomalous venous drainage. This is a rare anomaly and will not be considered in detail. Anatomically, all the veins from both lungs enter the right side of the heart, usually via a common pulmonary vein draining into a persistent left superior vena cava.

An atrial septal defect is obligatory, and the fully saturated blood from the lungs mixes with the venous blood in the right atrium. The mixed blood then passes through the [illegible]

and resemble radiologically the appearances seen in atrial septal defect. In some cases the pulmonary resistance is greatly raised as a result of the Eisenmenger reaction. According to Keith *et al.* (1958), the majority of infants under one year of age have extreme pulmonary hypertension, while cases studied at an older age usually have normal pressure or only slight hypertension.

When all the pulmonary veins drain into the superior cava the diagnosis may be strongly suspected if the catheter passes from the cava into the veins from both lungs. Dye dilution curves should show a longer appearance time from pulmonary artery than from right atrium; the reverse of the normal situation.

The radiological picture in such cases is characteristic, giving the "figure of eight" or "cottage loaf" appearance.

Ostium primum Defect: Persistent Atrio-ventricular Canal

This type of atrial septal defect lies low in the right atrium, overlies the tricuspid valve and has the ventricular septum as its lower margin When there is also a high ventricular septal defect and fission of the atrio-ventricular valves, the condition is known as a common atrio-ventricular canal (endocardial cushion defect).

This lesion is interesting from the aspect of the pulmonary circulation, for, unlike the septum secundum defect, severe pulmonary hypertension occurs at an early age. A left to right shunt is present at low atrial and high ventricular levels, and auscultatory evidence of mitral incompetence is common· the heart is usually very large and heart failure frequent. Mongolism may be associated, and infective endocarditis is not unusual. Many subjects die in infancy.

The reason for the higher levels of pulmonary pressure are not known. Possibly the presence of mitral incompetence and left ventricular failure precipitate pulmonary vasoconstriction as a result of left atrial hypertension, and thus an additional vasoconstrictive influence is added to that induced by hyperdynamic hypertension.

The characteristic cardiographic appearances have already been described in Chapter 7

Ventricular Septal Defect

Defects of the ventricular septum may occur in four main sites: immediately below the pulmonary valve; below the crista supraventricularis and related to the ventricular outflow tracts; near the inflow tract beneath the septal leaflet of the tricuspid valve; and near the apex of the septum. The size of the defect exerts a profound effect upon the pulmonary circulation, and is far more important, in most cases, than its position. From the functional standpoint defects may be divided into various categories:

1. Small defect, less than 5 mm diameter (Maladie de Roger) These patients have no abnormal features other than a loud pansystolic murmur at the lower left sternal edge due

to the very small left to right shunt. The pulmonary circulation is normal apart from the very small left to right shunt and such cases need no further consideration here.

2 Larger defects, 5–10 mm., associated with an appreciable left to right shunt, and pulmonary plethora. Pulmonary hypertension is absent, or if present is hyperdynamic in type. It is thought that an opening 10 mm. allows the maximum flow which the pulmonary vascular bed will take without a rise in pressure.

3 Large defects, 10–20 mm., associated with hyperdynamic and vasoconstrictive hypertension. Hypertension may be considerable and approach systemic levels, but the large left to right shunt persists, although there may be a minimal right to left shunt. Heart failure and respiratory infections are common, and often fatal in infancy in this group.

4. Large defects, 20 mm or larger with bi-directional shunt, and balanced pulmonary and systemic resistances (Eisenmenger reaction).

Classes 3 and 4 show considerable overlap—thus defects smaller than 20 mm. may show the Eisenmenger reaction, while larger defects may have severe pulmonary hypertension with persistence of a large left to right shunt. The Eisenmenger reaction does not apparently occur with defects of less than 10 mm (Selzer and Laqueur, 1951), and is usually associated with defects of 20 mm or over.

It is apparent therefore that the haemodynamic hazards of ventricular septal defect are heart failure and hyperdynamic vasoconstrictive hypertension on the one hand and the Eisenmenger reaction on the other

The origin of the root of the aorta. The aorta may have its origin entirely from the left ventricle, may over-ride the septal defect, or may arise from the right ventricle (transposition) The original suggestion that cases with an over-riding aorta constituted a separate group because they exhibited central cyanosis due to a right to left shunt is no longer tenable It is the level of the pulmonary resistance which determines a right to left shunt, not the position of the aorta, unless this is grossly dextroposed or transposed (Brotmacher and Campbell, 1958). This point is well illustrated by Keith *et al* (1958) who quote the case of a boy of seven years with a large defect well down from the aortic valve without aortic over-ride, who had equal systolic pressure in both ventricles and central cyanosis. In fact their patient was an example of the Eisenmenger syndrome without an over-riding aorta. Another of their cases, a baby of eight months, illustrated the converse. This infant had a septal defect measuring 10 mm. with 60–70 per cent aortic over-ride, yet the systolic pressure in the right ventricle was only 70 per cent of the systemic pressure, and apparently no right to left shunt was present According to Selzer and Laqueur (1951), the relation of the size of the defect to that of the aortic orifice is important in determining the haemodynamics and Selzer (1954) considered that the pressure differential between the two ventricles disappeared when the defect was larger than half the aortic orifice

Haemodynamics. The larger the defect the larger the left to right shunt and the higher the pulmonary artery pressure. This is an oversimplification, but a good general rule. When the defect is enormous, almost amounting to a single ventricle, the systolic pressures in the two ventricles are invariably equal. Under such circumstances the pulmonary vascular resistance must be at systemic level, and a small right to left shunt may occur. Cardiac catheterization demonstrates a rise in oxygen saturation in right ventricular as compared with right atrial blood. A frequent finding is a pressure gradient at infundibular level in

cases with a large defect and considerable pulmonary hypertension. The right ventricular systolic pressure may be two thirds of the systemic, with a gradient at infundibular level of from 10–50 mm. Hg, the pulmonary artery pressure still being elevated (Rudolph *et al.*, 1954; Eldridge and Hultgren, 1955a).

The cause of the gradient has been explained as resulting either from organic stenosis of congenital origin, or from a high flow of blood passing from an enlarged right ventricle through a normal-sized pulmonary valve. While these explanations are probably correct in some cases, personal experience suggests that some degree of infundibular obstruction exists in most cases in which a gradient is demonstrated. It is probable, however, that this obstruction is acquired rather than congenital. In a series of patients whose ventricular septal defects have been closed during total cardio-pulmonary by-pass at Hammersmith Hospital, one-third had infundibular obstruction, and one had valvular stenosis which consisted of a thick mass of hypertrophied muscle in the outflow tract (Cleland *et al*, 1958). This infundibular hypertrophy is likely to be part of the generalized right ventricular hypertrophy occurring with large defects. The obstruction to the pulmonary circulation thus produced may constitute an important protective mechanism to shield the pulmonary vascular bed from the effects of high pressure and flow. As will be seen later, it may explain why some patients with large defects do not develop the Eisenmenger reaction. The protective effect of pulmonary stenosis has been demonstrated in a child with a large ventricular septal defect, right ventricular hypertension, and partial stenosis of a branch of the right pulmonary artery. An angiogram showed normal small pulmonary arteries in the left lung, but constricted vessels beyond the pulmonary artery obstruction in the right lung (Chapter 6, Fig 66).

The left to right shunt in ventricular septal defect is revealed by dye dilution curves Injections made during catheterization of the right side of the heart, however, do not localize the site of the shunt. Injections of dye into left ventricle and aorta respectively will reveal the ventricular origin of the shunt (Swan and Wood, 1957).

In cases with transposition, dye dilution curves may be of great value in diagnosis, for an injection into the right ventricle will give a short appearance time if the aorta arises from this chamber, while from the left ventricle a longer appearance time will be obtained, as the dye passes into the pulmonary artery and through the lungs (Penido and Swan, 1957). Angiocardiography yields similar information.

Pulmonary hypertension in ventricular septal defect. Defects larger than 10 mm. are associated with sufficient pulmonary flow to produce hyperdynamic hypertension. In many cases vasoconstrictive hypertension is added, and high pressures reaching systemic [illegible] correlation between the age at death and the size of the defect, and four of their 25 patients who died in heart failure had small defects less than half the diameter of the aortic orifice.

In patients who survive infancy with moderate or large defects, pulmonary hypertension is likely to be progressive. Brotmacher and Campbell (1958) showed in their series of 25 patients that older patients had higher pressures in the group with pulmonary hypertension, but that this was not so in the patients with normal pulmonary pressures. They noted also a tendency for the pulmonary arterial pulse pressure to increase with age,

which they suggested might be due to decreasing distensibility of the pulmonary vascular bed Direct evidence in the same patient of a progressive rise in pulmonary artery pressure with age is scanty, but Adams *et al* (1955) reported seven patients who had been shown to develop a rise in pressure over a few years, and Brotmacher and Campbell (1958) quote the case of a boy of five whose pulmonary resistance increased from 8 to 23 units over a period of seven years

However, in children the pulmonary artery pressure may not necessarily rise progressively, for Downing (1959) reported that in patients who had been catheterized for a second time after an interval of from 17 months to 9 years, only a minority showed any rise in pressure, and in some infants the pressure even fell. His patients were aged 7 weeks to 17 years.

The size of the defect relative to the size of the heart may diminish with age, the infundibulum may hypertrophy, the defect close in systole, or the plane of the septum act in some way as a baffle to protect the lungs from left ventricular pressure and prevent further pulmonary vasoconstriction. But it is very possible that the pressure tends to rise more rapidly after the age of 20 years, especially in subjects with an initially raised pressure. The problems of progressive changes in the pulmonary circulation will not be fully understood until more is known of the evolution of the pulmonary vascular resistance with age in the normal subject.

Pulmonary hypertension does constitute a hazard, however, since it may be progressive, and a vicious circle may be postulated in large defects:

Excessive flow → hyperdynamic hypertension → reactive vasoconstriction → increased hypertension → medial hypertrophy of muscular pulmonary arteries → further hypertension → further medial hypertrophy → intimal damage → organic occlusive changes in small arteries → further hypertension → shunt reversal.

It is unlikely that the presence of slight arterial desaturation could contribute a hypoxic vasoconstrictive factor, since in general a right to left shunt is the consequence and not the cause of severe hypertension. Furthermore, Brotmacher and Campbell (1958) found that the rate of rise of pressure with age was greater in their acyanotic than in their cyanotic cases.

From the foregoing, it might be concluded that the Eisenmenger reaction (balanced systemic and pulmonary resistances, with right to left shunt) is of gradual onset over a period of years. That this may occur in some cases cannot be denied, but the weight of evidence strongly suggests that in most cases the reaction is determined at birth, as will be seen later

The development of changes in the pulmonary vessels in subjects with large defects is clearly of the first importance This problem has been beautifully presented by Edwards in the Lewis A. Connor Memorial Lecture for 1957 (Edwards, 1957) He points out that a small defect presents a high resistance to flow through it, and forms an obstruction to the torrential flow passing at systemic pressure from the left ventricle into the lungs The large defect, however, allows free communication between the ventricles and does not have the obstructive features of the small defect The direction of flow through the defect depends upon the balance between systemic and pulmonary resistances, the blood flowing more readily into the system with the lower resistance. If there is no obstruction to flow into the

lungs (such as infundibular hypertrophy or pulmonary stenosis) with a large defect, the changes develop in the pulmonary vessels. Normally at birth, the pulmonary vascula resistance falls precipitously. If this occurs in a patient with a large ventricular septa defect, the lungs will be flooded with blood at systemic pressure, with disastrous con sequences, and this is probably the reason for heart failure and death in very early life However, a safety mechanism exists, which presumably saves many patients. The pul monary arteries at birth have thick muscular coats and have the power of maintaining a high resistance, thus protecting the lungs, and preventing a left to right shunt of letha proportions.

Dammann and Ferencz (1956) have traced the pattern of the pulmonary vascular resistance in patients with large defects at various ages. The resistance tends to fall towards normal in the first few months of life, and then becomes fixed at a level lower than the systemic, but higher than normal. In time the resistance may rise further It is during the phase of falling pulmonary resistance that the danger of death from heart failure is greatest.

Edwards (1957) has found that the pulmonary vessels are normal when the defect is small, but are always abnormal when the defect is large. He has described three types of pulmonary vascular bed:

1. High resistance—high reserve.
2. High resistance—low reserve.
3. Transitional form.

Type 1 has the characteristic of the normal foetal vascular bed, the muscular arteries showing thick muscular medial coats, with thick elastic laminae, the arterioles showing similar appearances, and often well-defined elastic layers also. Intimal lesions are minimal In such patients, pulmonary resistance is above normal adult levels, as a result of vaso-constriction. The term *high reserve* denotes the ability of the vessels to dilate and increase the capacity of the vascular bed.

Type 2 is entirely different, with characteristic obliterative lesions in the large muscular arteries due to intimal thickening and hyalinization The small muscular arteries are mostly thin-walled and dilated Serial sections show irregular deposition of young connective tissue, causing a narrowing and irregularity of the lumen. Organized thrombi may be present as a secondary phenomenon This type of vascular bed has been alluded to already in relation to atrial septal defect, and the intimal lesions have been described in Chapter 6. It has been suggested that the intimal lesions and dilatations of the vessel wall are in reality arterio-venous communications and that a shunt through these channels is a contributory cause of central cyanosis. Evidence from dye dilution curves denies this possibility, and the presence of fully saturated blood in the left atrium indicates that central cyanosis is not pulmonary in origin.

In the high-resistance–low-reserve type of vascular bed, the atrophy and dilatation of vessels is usually distal to areas of obstruction, the obstructive changes giving rise to the high vascular resistance Edwards considers that the vascular bed has reached the limits of its capacity, hence the term *low reserve*.

The high-resistance–high-reserve type is considered to represent persistence of the normal foetal vascular pattern in response to the presence of a large ventricular septal

defect. The low-reserve type, by contrast, represents the complication of long-standing severe pulmonary hypertension.

Probably, as Edwards suggests, the former type yields to the latter with the passage of time, for among subjects with large defects, only the high-reserve vascular bed has been found in those under two years of age. This pattern may persist for a considerable time, but rarely into adult life. Nearly always in adults with large defects the vascular bed is of the low-reserve type.

The importance of right ventricular outflow tract obstruction. In large defects, when the left ventricle communicates with the pulmonary vascular bed, the patient is in great danger of left ventricular failure unless some hindrance to torrential pulmonary flow is present. Vasoconstriction and failure of the high foetal pulmonary resistance to fall precipitously at birth probably saves a number of infants. In the absence of this protection, the presence of pulmonary stenosis can produce the same effect. If the obstruction is moderate, a nice balance may be struck between the pulmonary flow on the one hand, and the presence of a right to left shunt on the other. When the stenosis is severe, the lungs are underfilled and there is a large right to left shunt, producing a picture resembling the Tetralogy of Fallot. Conversely, minimal stenosis will not constitute an effective obstruction to the left ventricle. But as has been mentioned, many cases do not have pulmonary stenosis in the accepted sense, but merely a hypertrophied infundibulum. This hypertrophy may be lifesaving, as is suggested by the following case. A man of 25 had a very large ventricular septal defect, measuring 3.5 × 3.5 cm, which was associated with a grossly hypertrophied infundibulum, producing a gradient of 30 mm Hg across the outflow tract of the right ventricle. The pulmonary valve was incompetent. He had a large left to right shunt but had never been in heart failure. With a defect of this size either early heart failure or the Eisenmenger reaction would have been expected. It is postulated that this infundibular hypertrophy protected his lungs. This concept is the basis of the operation proposed by Dammann and Ferencz (1956) who suggested that the production of critical pulmonary stenosis might improve patients in whom the septal defect could not be closed. By contrast, adult patients are sometimes seen who have a large pulmonary blood flow, but no pulmonary hypertension and no infundibular obstruction. Presumably in these patients some other factor, perhaps the angle of the ventricular-septum or closure of the defect in systole, has deflected the full force of the left ventricle from the pulmonary vessels so that neither the Eisenmenger reaction nor heart failure has occurred in early life.

The infundibular hypertrophy found in many cases of ventricular septal defect is considered to be acquired during the process of ventricular hypertrophy and if this is so, is not therefore a true developmental abnormality. It should be distinguished from the true infundibular stenosis which is due to imperfect formation of the infundibulum during early foetal life.

Clinical features of ventricular septal defect. In the minimal defect (Maladie de Roger), symptoms are absent, and the only abnormal physical sign is the pansystolic murmur, often with thrill, which is heard at the left lower sternal edge. The sole risk, as far as is known, is infective endocarditis.

With larger defects, infancy is a particularly troublesome period; feeding difficulties, slow gain in weight and severe respiratory infections are common. After the age of one year, patients often improve and in childhood effort tolerance may be surprisingly good,

but physical development is poor, and respiratory infections are still frequent. The physical signs are more striking than the symptoms. The pulse is small and jerky in quality,

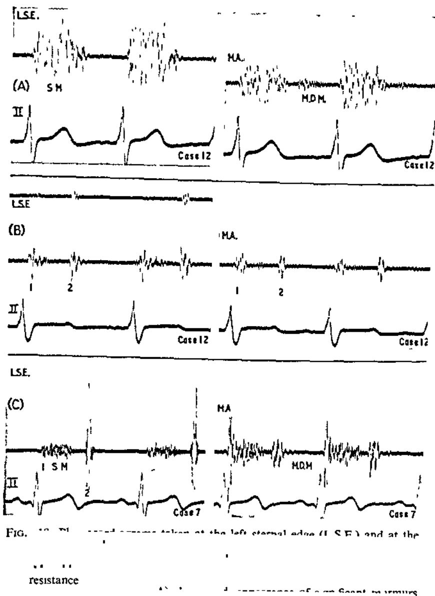


FIG. [illegible] left sternal edge (L.S.E.) and at the [illegible]

resistance [illegible] murmurs

and the jugular venous pressure normal or slightly raised, the "a" wave being only slightly prominent. The cardiac impulse is left ventricular in type, with a hyperdynamic thrust· the right ventricle is commonly also enlarged. The loud pansystolic murmur due to the left

to right shunt at ventricular level is accompanied by a thrill, and there is an apical mid-diastolic murmur attributed to excessive mitral valve flow and turbulence (Fig. 118a). The second heart sound is usually accentuated, and the split wider than normal. An ejection murmur due to pulmonary flow may be heard, but is often obscured by the murmur of the defect. There is often bulging of the left side of the sternum

When pulmonary hypertension is considerable, the mitral flow murmur is shorter and softer or may be absent. The defect murmur and thrill may be shorter, and the pulmonary closure sound louder (Fig 118c) The features of extreme hypertension will be discussed under the Eisenmenger syndrome.

Pulmonary stenosis is often difficult to detect, but it may be suspected if the pulmonary closure sound is unduly soft and delayed and an ejection murmur audible in the pulmonary area. Outflow tract obstruction due to "acquired" infundibular hypertrophy cannot be diagnosed clinically with certainty.

The radiological and cardiographic features are discussed in Chapters 5 and 6.

Associated lesions. Apart from pulmonary stenosis, there may be aortic incompetence, patent ductus arteriosus, or pulmonary incompetence. Aortic incompetence is a well-recognized accompaniment, occurring in three of Brotmacher and Campbell's (1958) 75 patients It is usually due to a high (supracristal) defect which deforms one of the aortic cusps (Scott *et al*, 1958). A patent ductus was more common in the Hammersmith series of patients operated on for closure of the defect than expected, occurring in 10 per cent. Diagnosis is difficult and may be impossible, even with the aid of catheterization, for the typical continuous murmur is exceptional, and evidence of an additional left to right shunt at pulmonary artery level often absent. It may be suspected if the pulmonary artery is unduly large, or if an early diastolic murmur can be heard down the left sternal edge. But, of course, this can be due to pulmonary or aortic incompetence (Cleland *et al.*, 1958)

It has been postulated that in many cases the left to right shunt occurs almost entirely at ventricular level, there being little flow through the duct. Elevation of pulmonary resistance would reduce the shunt, and abolish the typical signs of patent ductus. Whatever the cause, patent ductus can be a silent lesion in the presence of a ventricular septal defect (Cleland *et al*, 1958), and may require aortography for preoperative diagnosis (Chapter 5)

Pulmonary incompetence may result in a low diastolic pressure in the pulmonary artery approximating to that in the right ventricle. It may be suspected clinically if there is a high-pitched early diastolic murmur down the left sternal edge which increases with inspiration Pulmonary incompetence occurred in 19 of Brotmacher and Campbell's (1958) 75 patients, and was well tolerated by the patients.

Complete heart block is less common than is often thought, and occurred only in one of the 75 patients in Brotmacher and Campbell's series. When present it suggests the possibility of corrected transposition of the great vessels.

Shunts at pulmonary artery level

1. *Patent ductus arteriosus.*
2. *Aorto-pulmonary defect.*

Patent ductus arteriosus is by far the commoner of these two lesions. The pulmonary

circulation does not differ significantly in the two conditions, and only patent ductus will be discussed further.

Much of what has already been said about ventricular septal defect applies also to patent ductus, but of course the ductus is a normal structure which only exerts abnormal effects when it fails to close after birth. Dawes *et al.* (1953, 1955) showed that a 90 per cent fall in pulmonary vascular resistance occurs with the onset of respiration, followed by constriction of the ductus. A left to right shunt, however, persists for from 12 to 48 hours.

In humans the ductus remains patent, with a right to left shunt, for from three hours to three days in an appreciable number of normal mature infants (Eldridge and Hultgren, 1955b). The pulmonary artery pressure may remain elevated for up to one week after birth, and this of course tends to prevent closure of the ductus (Rowe and James, 1957).

The reasons for normal closure of the ductus are not fully understood. Dawes (1956) considers the rise in oxygen tension of the arterial blood to be an important factor in causing constriction of the ductus in lambs, while Alzamora *et al.* (1953) showed that patent ductus was common in patients born at high altitudes If hypoxia were responsible for persistent patency, however, one would expect to find a higher incidence of patent ductus in infants with respiratory distress, atalectasis or hyaline membrane disorder, but this is not the case. Damage to the growing foetus by maternal rubella has an association with persistent patency of the ductus (and pulmonary stenosis) but the exact relationship to hypoxia is not known (Heiner and Nadas, 1958).

In childhood, patent ductus usually produces little in the way of symptoms, although retarded physical development is common. In adults, symptoms such as tiredness and dyspnoea are usually present after the age of 30 years. Anginal pain may occur (Fairley and Goodwin, 1959).

In infancy, about 12 per cent develop serious symptoms: failure to thrive, dyspnoea, respiratory infections and congestive heart failure (Keith *et al.*, 1958).

Haemodynamics and the pulmonary circulation. A left to right shunt through the ductus is the usual rule, the volume being directly proportional to the size of the duct, and inversely proportional to the pulmonary vascular resistance, which usually falls dramatically after birth. When it remains elevated, the shunt may be reversed, giving rise to the Eisenmenger syndrome at ductus level.

As a result of the left to right shunt there is enlargement of the major pulmonary arteries, *of the aorta, and of the left atrium.*

Pulmonary hypertension may occur as a result of four main factors: torrential pulmonary flow; vasoconstriction; increased pulmonary venous pressure due to left ventricular failure; and obstructive changes in the small pulmonary vessels. These changes consist of medial hypertrophy and intimal proliferation (Heath and Whitaker, 1956)

The factors which produce vasoconstriction and later organic vascular obstruction are presumed to be the same as those in ventricular septal defect and need not be considered again.

Progressive pulmonary hypertension in patients with a large ductus and high pulmonary flow is not inevitable. In a series of 40 adults, the pulmonary arterial pressure was raised in only nine of 17 patients in whom it was measured, and there was no direct relation between age and pulmonary vascular resistance (Fairley and Goodwin, 1959).

The size of the ductus is of importance in determining the course of the disease, and a close parallel may be drawn with ventricular septal defect. With small ducts, the lumen is such that it acts as an obstruction between left ventricle and pulmonary vascular bed, as with a small ventricular septal defect. The pulmonary vessels are protected, and are thus histologically normal When the duct is larger, and the pulmonary blood flow considerable, there is a danger of heart failure in infancy, and if infancy is survived, of progressive pulmonary hypertension due to reactive vasoconstriction, followed by medial hypertrophy and intimal changes in the small vessels. In this group, as with the large ventricular defects, the pulmonary artery pressure may tend to rise with age, although as has been mentioned, this does not always happen. In many such patients, pulmonary hypertension is labile, for at thoracotomy compression of the ductus often causes a dramatic fall in pulmonary artery pressure. The pressure, however, may not fall if organic pulmonary vascular disease is advanced, and some hypertensive patients have a small right to left shunt in addition to the left to right shunt Finally, the very large, wide ductus results in the lungs being in communication with the left ventricle, and is usually associated either with heart failure in infancy, or with the development of the Eisenmenger reaction, where pulmonary artery and aortic pressures and resistances are balanced and the shunt reversed

Cardiac catheterization reveals a higher oxygen saturation in the pulmonary artery than right ventricle, and the ductus may be entered with the catheter in many cases if the left pulmonary artery is probed. The catheter then passes down into the descending aorta. Herein lies an important distinction from an aortic-pulmonary "window", for when the catheter has passed through the "window" it commonly enters the ascending aorta, thus passing upwards and not downwards.

Occasionally samples from the right ventricle are also more highly saturated than mixed venous blood, as a result of associated pulmonary incompetence, so that a ventricular septal defect may be simulated

The pulmonary artery pressure is usually well below that of the aorta, and often normal. In patients with larger ducts, however, it may approach or reach aortic levels, when intermittent shunt reversal may occur. Shepherd *et al.* (1954) have described alterations in the shunt through the ductus in systole and diastole in a patient with bi-directional shunts, the oxygen saturation in the pulmonary artery being higher in systole than in diastole, showing that the left to right shunt was greater in systole

Indicator dye dilution studies show a left to right shunt at all levels in the right side of the heart and pulmonary artery. If reversal of flow is occurring, the right to left shunt will also appear in curves made from injections from all right heart chambers, and pulmonary artery, and will thus indicate that the shunt is at pulmonary artery level

Associated lesions Keith *et al* (1958) list eight associated lesions found in 28 children when ducts were closed surgically The commonest anomalies were co-arctation of the aorta, and ventricular septal defect Pulmonary stenosis with patent ductus has been reported by Heiner and Nadas (1958) in children with extra-cardiac congenital anomalies due to rubella. Bonham-Carter *et al.* (1955) reported eight patients with co-existing aortic valve disease, in two of whom there was a history of maternal rubella.

Co-arctation of the aorta does not significantly alter the haemodynamics unless the ductus is inserted distal to the co-arctation and the pressure in the aorta below it is less than in the pulmonary artery, so that blood shunts from pulmonary artery to aorta.

Ventricular septal defect with patent ductus has already been discussed. Pulmonary stenosis, if of any severity, reduces the pulmonary vascular resistance and favours the left to right shunt. It does not protect the lungs as in ventricular septal defect, for the shunt occurs distal to the obstruction.

The clinical picture of patent ductus arteriosus. Patients are often small for their age. The classical cardiovascular signs are present: increased pulse pressure, water hammer pulse of good volume, hyperdynamic left ventricle, and continuous murmur (and often thrill) maximal at the base of the heart over the pulmonary artery. There is commonly some enlargement of the right ventricle, but this never marked unless pulmonary hypertension or stenosis is appreciable. The second heart sound is usually well heard, and the pulmonary component is loud if pulmonary hypertension is present. The split is normal or slightly widened. A rumbling apical mid-diastolic murmur, attributed to torrential

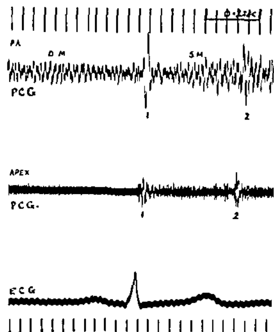


FIG 119 Phonocardiogram (P C G.) in patent ductus arteriosus
1 = 1st heart sound
2 = 2nd heart sound
SM = systolic component of murmur
DM = diastolic component of murmur
PA = pulmonary area
Apex = cardiac apical impulse
The continuous murmur is clearly seen, and is maximal at the 2nd heart sound

mitral valve flow, is the rule in most cases. The ductus murmur is maximal in late systole, when flow between pulmonary artery and aorta is greatest, and diminishes in diastole when flow is less (Fig. 119). In infants the diastolic murmur is frequently absent, only a systolic murmur being present.

When pulmonary hypertension is considerable, there is a marked parasternal lift, due to right ventricular enlargement and the pulmonary closure sound is loud. The apical mid-diastolic murmur may be soft and short and in some cases the characteristic continuous ductus murmur is replaced by short systolic and early diastolic murmurs, because the left to right shunt has been reduced by pulmonary hypertension, and is insufficient to give a murmur throughout the cardiac cycle.

When pulmonary stenosis is present, the pulmonary closure sound is soft and delayed, but the systolic murmur of stenosis may be obscured by the ductus murmur. The right ventricle is enlarged. Proof of pulmonary stenosis may not be possible without catheter-

ization, which shows a gradient across the pulmonary valve. False gradients and acquired infundibular hypertrophy do not apparently occur in patent ductus.

The cardiographic and radiological appearances have been discussed in previous chapters.

Some Rarer Forms of Congenital Heart Disease associated with an Increased Pulmonary Blood Flow

This group includes transposition of the pulmonary artery and aorta, which may be associated with shunts at atrial, ventricular or duct level, or with tricuspid atresia. Other conditions are persistent truncus arteriosus, in which large "pulmonary arteries" arise directly from the single outflow tract, and aorto-pulmonary "window", in which there is a fistula between the great vessels at the root of the aorta. In persistent truncus bronchial arteries may also be well developed, but less so than in patients with extreme reduction in pulmonary blood flow.

In complete transposition the pulmonary artery arises from the left, and the aorta from the right, ventricle. Several different types of shunt may occur, in order to cross the two circulations There may be a right to left shunt through a foramen ovale or atrial septal defect, and also through a patent ductus. When a ventricular septal defect is present, the shunt is usually from right to left, but may be bi-directional. In most cases the lungs are markedly overfilled and the pulmonary arteries enlarged There are no other special features relevant to the pulmonary circulation Transposition may, however, be associated with reduced pulmonary blood flow, either as a result of associated pulmonary stenosis (Cleland *et al*, 1957) or of the Eisenmenger reaction. The former condition resembles the Tetralogy of Fallot clinically, with certain important differences

Cardiac catheterization shows identical oxygen saturations in the right ventricle and in the aorta. The aorta is easily entered by the catheter from the right ventricle, but the pulmonary artery is difficult to enter. Dye dilution curves assist diagnosis by showing a rapid appearance time and left heart type of curve from an injection in the right ventricle (Penido and Swan, 1957, Oakley *et al.*, 1960).

Angiocardiography, however, is the most helpful diagnostic method (Chapter 5)

The degree of dyspnoea and cyanosis is usually proportional to the pulmonary blood flow in patients with several compensatory anomalies and a high pulmonary flow, who may be surprisingly tolerant of exertion and only slightly cyanosed.

THE EISENMENGER SYNDROME

This eponymous term owes its inception to a case of large ventricular septal defect and overriding aorta described by Dr. Victor Eisenmenger in 1897. For many years the term was used to label patients with anatomical over-riding aorta and a large ventricular septal defect, but without pulmonary stenosis, and it was thought that such patients, who were usually cyanosed, constituted a distinct type of ventricular septal defect. The fallacy of this view was suggested by Selzer and Laqueur (1951), who pointed out that uncomplicated ventricular septal defect and the Eisenmenger type were merely different degrees of

the same developmental abnormality, and that the latter was always associated with a large defect and usually with balanced systemic and pulmonary arterial pressures. Brotmacher and Campbell (1958) showed that, unless the aorta arises entirely from the right ventricle, the presence of a right to left shunt and central cyanosis depends entirely upon the relative pressures in the two ventricles, and not upon the position of the aortic root.

Wood (1958b) has shown that the syndrome consisting of extreme pulmonary hypertension with right to left shunt presents a similar clinical picture whatever the level of the shunt. He has proposed that the term Eisenmenger syndrome should be retained for such cases, and used to describe a haemodynamic rather than an anatomical anomaly The principal lesions which were associated with the Eisenmenger syndrome in his series are listed below.

Diagnosis	*Frequency of Eisenmenger syndrome*	*Total number of cases*	*Site of shunt*
Patent ductus	16%	180	Pulmonary/aortic
Aortic pulmonary "window"	60%	10	Pulmonary/aortic
Persistent truncus arteriosus	100%	4	
Complete or corrected transposition (with V S D.)	66%	15	Ventricular
Single ventricle	100%	6	
Ventricular septal defect (V.S D)	16%	136	
Ostium primum defect or atrio-ventricular canal	*43%*	*21*	Atrial
Atrial septal defect	6%	324	
Total anomalous pulmonary venous drainage	*17%*	*6*	

(Modified from Wood, 1958b)

Of major interest are the commoner lesions causing shunts at atrial, ventricular and pulmonary artery level, and the Eisenmenger reaction will be considered in relation to atrial septal defect, ventricular septal defect and patent ductus arteriosus.

It will be seen from Wood's figures that the Eisenmenger reaction is three times as common in ventricular septal defect and patent ductus as in atrial septal defect. Furthermore, it seldom, if ever, occurs unless the abnormal communication is large The minimum size in his 53 autopsy cases was 0·7 cm., 1·5 cm., and 3 cm for aorto-pulmonary, ventricular, and atrial communications respectively. The Eisenmenger syndrome occurred in 50 per cent of patients with large patent ductus and large ventricular septal defects Finally, the age of onset was in infancy in around 80 per cent of cases of ductus and ventricular defect, and in adult life in 90 per cent of cases of atrial defect

These figures show conclusively that there is a sharp difference between the behaviour of shunts at ventricular and pulmonary artery level on the one hand, and at atrial level on the other, in respect of the Eisenmenger syndrome.

The Genesis of the Eisenmenger Syndrome

In order to discuss this difficult problem it is necessary to consider the pulmonary circulation in the foetus and in early infancy.

Wood (1958b) estimates that the foetal pulmonary vascular resistance at birth must be extremely high, about 500 units, because the pulmonary blood flow is exceedingly small, and the pulmonary artery pressure equal to that of the aortic at around 50 mm. Hg. In the newborn infant the pulmonary resistance is presumably the same as the systemic, for the ductus regularly shunts from right to left during the first three hours of life (Eldridge and Hultgren, 1955b) The lungs are functional at this time, and the cardiac output is approximately 0·5 litres/min. (Prec and Cassels, 1955), so that the pulmonary resistance probably falls to 100 units, assuming that the pulmonary flow has increased four-fold and the pressure remains unchanged.

The amazingly high pulmonary vascular resistance at birth may be due to coiling and kinking of the pulmonary vessels in the non-aerated foetal lung. Such vessels would presumably be highly resistant to flow, but their resistance would be expected to fall as the lungs expand, and the vessels uncoil (Dawes, 1959). The blood flowing through the vessels would force them to dilate, and they may thus be likened to erectile tissue. Jäykkä (1957) has claimed that the capillary vessels when distended with blood help to hold out the alveoli and expand them to their proper extent, although recent views incline to the opinion that the lungs expand as a result of external and chemical stimuli, and that the alveoli then open, the capillaries unfold, resistance falls and the capillaries become filled with blood (Lancet, 1959). But Bonham-Carter *et al.* (1956) have shown that a high central venous pressure is beneficial to immature newborn babies, and have suggested that a high cardiac output is necessary to drive blood through the high resistance pulmonary vascular bed, dilate the capillaries, and open up the alveoli. Hypoxia at this stage seems to be a vital factor, which tends to increase pulmonary resistance, impede the flow of blood through the lungs, and therefore hinder adequate alveolar function. Impaired alveolar function would lead to further hypoxia, so that a vicious circle might be set up But usually, with good initial breaths, the lungs expand well, the vascular resistance falls, and the high cardiac output forces blood through the vessels, which dilate so that the resistance falls still further. The high output is probably due largely to a transfusion of blood from the placenta to the baby in the third stage of labour (Gunther, 1957) Lind and Wegelius (1956) have shown a stepwise diminution in heart size during the first two or three breaths which would be consistent with a fall in initial high right atrial pressure and venous return as the lungs expand and the pulmonary vascular resistance diminishes

Certainly, the fall in pulmonary vascular resistance at birth seems to be closely associated with expansion of the lungs The suggestion that the extreme resistance in the foetus is due to hypoxic vasoconstriction is sternly criticized by Wood (1958b) on the grounds that the resistance can fall equally rapidly if the lungs are inflated with nitrogen (Dawes *et al*, 1953) But possibly the high right atrial and ventricular pressures, and the high cardiac output are sufficient to overcome vasoconstriction. In any event, expansion of the lungs must presumably reduce resistance by its uncoiling effect on the vessels, as already mentioned.

When the pulmonary vascular resistance has fallen sharply to systemic levels, it

remains there temporarily, and falls to normal levels slowly (Wood, 1958b). The reason for this delayed fall may be the thick muscular media of the pulmonary arteries, which have developed in response to the systemic pressure to which they have been subjected (Edwards, 1957; Wood, 1958b). The thick media also suggests that they are in a state of active vasconstriction (Edwards, 1957). Only a small amount of the blood which leaves the right ventricle of the foetus enters the pulmonary vascular bed, most of it being shunted through the ductus into the aorta *In order for this shunt to occur there must be a high resistance to* flow in the pulmonary vascular bed. Therefore pulmonary hypertension with right to left shunt is the normal situation in the foetus. This is exactly the definition of the Eisenmenger syndrome. It will be remembered that the "high resistance—high reserve" pulmonary vascular bed described by Edwards (1957) in patients with large ventricular septal defects and severe pulmonary hypertension is very similar to that of the normal foetus.

It follows that the pulmonary vasculature in the Eisenmenger syndrome is almost identical with that of the normal foetus, until secondary occlusive changes and intimal necrosis have occurred in the former. Heath (1959) has shown that the elastic laminae in the large elastic pulmonary arteries are compact and dense, as in the aorta, in cases in which the Eisenmenger reaction has been established from birth

It is necessary to seek the reasons why, in certain patients with abnormal communications at pulmonary artery, ventricular, or atrial level, the pulmonary resistance *fails* to fall and the vasculature to change to the adult type.

According to Wood (1958b) the situation in the normal infant is as follows: increased alveolar oxygen tension promotes vasodilatation, which is met by increased flow from aorta to pulmonary artery, and this flow tends to maintain pulmonary artery pressure at systemic level. When the ductus closes, the flow is reduced, and the hyperdynamic factor is removed The pressure in the pulmonary artery therefore falls, and vasoconstriction diminishes From then on the muscular medial coats of the small arterioles gradually involute, reaching the adult type in about three months (Edwards, 1957).

The importance of the cessation of high pulmonary flow gives the clue to the Eisenmenger syndrome. If an abnormal defect is present which permits a pulmonary flow large enough to maintain pulmonary artery pressure at systemic level, the foetal type of pulmonary vasculature persists and the Eisenmenger syndrome is established. It does not matter whether the defect is at pulmonary artery or ventricular level

This explains why the defect is always large, and why the Eisenmenger reaction is usually established at birth (Wood, 1958b).

Clearly the size of the defect is critical, and some intermediate cases occur in which the foetal vasculature only partially involutes, giving rise to a high pulmonary vascular resistance associated with a high flow and sometimes minimal right to left shunt For some reason, all cases with a large defect do not develop the Eisenmenger syndrome, and many patients are overwhelmed by the torrential pulmonary blood flow and die shortly after birth.

Fig. 120 shows the pulmonary blood flow and pressure in 42 cases of congenital heart disease. Most of the patients fall into two definite groups: high flow with low pressure, and low flow with high pressure respectively Most of the latter are in the Eisenmenger category. There are, however, *some cases intermediate* between the two groups, which could be described as "partial" Eisenmenger syndromes.

The true Eisenmenger syndrome requires more precise definition, for patients with large left to right shunts, equal systemic and pulmonary artery pressures, and minimal arterial desaturation are not infrequently seen. They come within the present definition of the syndrome, but represent a different haemodynamic situation. Moreover, these patients can sometimes be successfully treated by closing the defect, in contradistinction to the true Eisenmenger syndrome. The following exact definition is therefore proposed: "The Eisenmenger syndrome: severe pulmonary hypertension with balanced systemic and pulmonary vascular resistances, central cyanosis, and a trivial or absent left to right

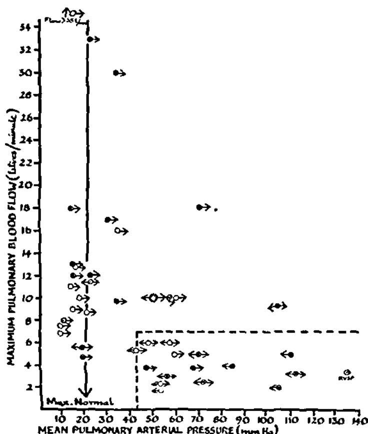


FIG 120 Total pulmonary blood flow and mean pulmonary artery pressure in congenital heart disease

● Patent ductus arteriosus
○ Atrial septal defect
⊗ Ventricular septal defect
→ Left to right shunt
← Right to left shunt
←→ Bidirectional shunt
RVSP Right ventricular systolic pressure

(From Goodwin (1958))

shunt." The latter portion of the definition would also cover cases of atrial septal defect with pulmonary resistance lower than systemic

The Eisenmenger Syndrome in Atrial Septal Defect

The sharp difference between incidence and age of onset of the syndrome in atrial defects and ventricular defects and patent ductus has yet to be explained. Wood (1958b) believes that there is no interatrial shunt during the critical neonatal period, possibly

because the right ventricle is powerful and dominates the left and exerts a high resistance to filling. As has already been mentioned, the shunt from left to right atrium occurs chiefly because of the lower resistance to filling of the right as compared with the left ventricle. In early neonatal life resistance to filling and diastolic tone are balanced in both ventricles

If no interatrial shunt exists at this time, there is no reason why the pulmonary vascular bed should not involute normally, and Wood considers that this involution occurs before any appreciable left to right shunt is established between the atria.

But it is difficult to understand, if this reasoning is correct, why the Eisenmenger syndrome ever develops in atrial septal defect. A number of cases continue to have a very large pulmonary blood flow for many years, and die from congestive heart failure, without extreme pulmonary hypertension. In the small number of cases in which the syndrome develops, it does so presumably because the hyperdynamic hypertension causes damage to the pulmonary vessels before complete involution of the pulmonary vascular system has occurred, or, as Dexter (1959) suggests, the high pulmonary flow leads to right ventricular failure which causes stagnation and thrombosis in the pulmonary vessels Intimal fibrosis and thrombotic lesions develop subsequently.

The protective influence of right ventricular outflow tract obstruction has already been mentioned, and it is particularly interesting that pulmonary stenosis never seems to occur in the Eisenmenger syndrome. Because of this, Dammann and Ferencz (1956) have adopted the practice of producing pulmonary stenosis in order to reduce the pulmonary hypertension and initiate involution of the pulmonary vascular bed The operation must, of course, be performed before secondary occlusive changes have occurred in the vessels

Cardiac Catheterization in the Eisenmenger Syndrome

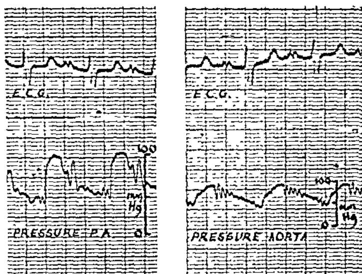
Catheterization reveals balanced pulmonary artery and systemic pressures and resistances (Fig. 121) There is usually a small bi-directional shunt present and the site reveals the level of the defect. In cases of patent ductus, the catheter frequently enters the aorta from the pulmonary artery, for the duct is wide and short. When the defect is at ventricular level the catheter may pass into the aorta from the right ventricle. The pulmonary capillary wedge pressure is invariably normal, except in cases of total anomalous pulmonary venous drainage.

Indicator dye dilution curves will show usually a definite right to left shunt but may fail to reveal the left to right shunt The double humped curve characteristic of a right to left shunt can be seen when the dye is injected into a chamber proximal to the site of the defect, but not in one distal to it. In this way, the site of the defect can be determined (Oakley *et al*, 1960) (Fig 122).

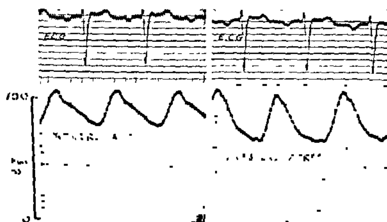
Clinical Features

In cases of patent ductus and of ventricular septal defect, mild cyanosis may be recognized early, but is often not appreciated. Clubbing is slight, but both cyanosis and clubbing were more marked in Wood's (1958b) cases of ventricular septal defect than of patent ductus. Polycythaemia is variable. Effort intolerance is often only slight or moderate

Other symptoms include haemoptysis, angina, and syncope Haemoptysis is related to pulmonary thrombosis and infarction, and angina and syncope to low cardiac output Congestive heart failure may occur terminally.



(a)

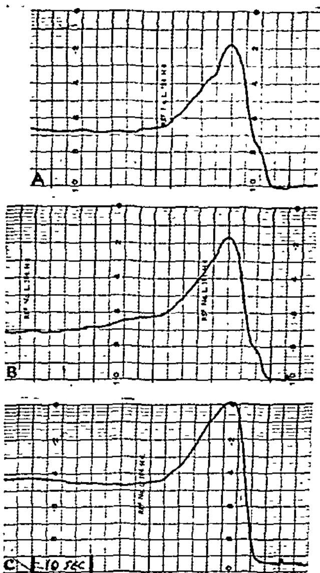


(b)

FIG 121 Balanced pulmonary and systemic (aortic) pressures in the Eisenmenger syndrome
(a) Ventricular septal defect (Catheter passed into aorta from right ventricle)
(b) Patent ductus (Catheter passed into aorta from pulmonary artery (PA) through ductus)

The physical signs are those of considerable pulmonary hypertension and have been outlined in Chapter 4. The jugular venous pulse usually shows a moderate "a" wave, except in atrial defects, when it may reach larger proportions. A large systolic wave from tricuspid incompetence occurs in a small proportion

The arterial pulse is small or normal and the cardiac impulse usually tapping and diffuse, but there may be a parasternal lift in patients with atrial septal defect, due to



shown

dilatation of the right ventricle. A right atrial gallop is commonly heard together with a pulmonary systolic ejection murmur and click. The second heart sound is loud, and very narrowly split, except in some cases of atrial defect, when the split may be wider.

The site of the defect is sometimes difficult or impossible to determine at the bedside. Certain pointers, however, may be of value. A history of late onset of cyanosis, especially in a female, favours an atrial defect, as does the presence of arachnodactyly or other stigmata of Marfan's syndrome. A history of maternal rubella favours a patent ductus.

Patent ductus arteriosus with the Eisenmenger reaction may sometimes be readily diagnosed clinically by the phenomenon of differential cyanosis and clubbing Since the duct enters the descending aorta, unsaturated blood from the pulmonary artery tends to be deflected to the lower extremity, while oxygenated blood from the left ventricle passes to the head and neck. Hence the toes may be blue and clubbed, but not the hands. The differences are often not striking, and arterial samples from brachial and femoral arteries



FIG 123. Differential clubbing (toes only) in patent ductus with reversed shunt (Eisenmenger type).

may be required to show the higher oxygenation in the upper extremity Occasionally desaturated blood may pass into the left sublavian artery, giving rise to cyanosis in the left hand. Peripheral cyanosis in the feet due to cold may be excluded by comparing the hands and feet after immersion in a warm bath (Fig. 123)

Needless to say, when the ductus shunt is reversed, the typical murmur disappears completely

Narrow splitting of the second heart sound occurs in both patent ductus and ventricular septal defect, but wide splitting is not uncommon in atrial defect, and is often fixed The second heart sound therefore is of some value in distinguishing atrial septal defects from patent ductus and ventricular septal defects.

The radiological features are described in Chapter 5, and the cardiographic signs in Chapter 7, while prognosis has already been mentioned in Chapter 4.

The Effect of Drugs and Oxygen on the Pulmonary Circulation in Pulmonary Hypertension due to Congenital Heart Disease

Several drugs have been used in an attempt to lower pulmonary artery pressure and resistance, but with little success. Doyle *et al.* (1957) reported that hexamethonium failed significantly to lower the pulmonary resistance in seven patients with severe pulmonary hypertension, six of whom had a reversed shunt. However, in one case the arterial oxygen saturation increased very slightly (four per cent) (Fig. 124)

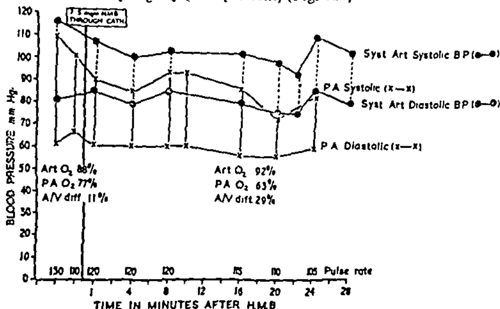


FIG [illegible]

Rudolph *et al.* (1958) reported that priscoline failed to lower pulmonary vascular resistance in eight patients with severe pulmonary hypertension and lone left to right shunts, and produced only a slight fall in one other patient. However, Blount and Grover (Blount, 1959) have reported a selective fall in pulmonary arterial pressure, with increase in the left to right shunt in a 13-month-old infant with a ventricular septal defect and pulmonary hypertension It is possible that young children and infants may be more responsive to drugs than older children and adults.

Wood (1958b) has been unable to produce any pulmonary hypotensive effect with acetylcholine, priscoline or aminophylline in patients with the Eisenmenger reaction over the age of five years. This contrasts strikingly with the ready fall in pulmonary resistance which he has reported in patients with other forms of pulmonary hypertension and which has been discussed in Chapter 4. Measurements of changes of pulmonary pressures and shunts in acute observations are exceedingly difficult to make with accuracy, however, owing to the large number of variables involved.

Acetycholine has, however, been shown by Shepherd *et al.* (1959) to dilate the pulmonary vessels in patients with pulmonary hypertension due to atrial and ventricular septal defects.

Edwards (1957) has reported a fall in pulmonary vascular resistance in infants under the age of two years on breathing oxygen. By contrast, Burchell *et al.* (1950) were unable to lower the pulmonary artery pressure or alter the shunt with 100 per cent oxygen in adults and in children over the age of five years, although inhalation of ten per cent oxygen raised the pulmonary resistance and increased the right to left shunt, in certain cases (Burchell *et al.*, 1953).

In congenital pulmonary hypertension medical measures to lower the pulmonary resistance produce inconstant and variable effects in acute observations. Personal experience of attempts to treat patients on a long-term basis with priscoline, aminophylline and ganglion blocking agents has been extremely disappointing. Four adult patients and one child with the Eisenmenger syndrome were treated for periods of from three months to two years with ganglion blocking agents. There was no reduction in dyspnoea or cyanosis, and no increase in arterial oxygen saturation. The venous pressure did not fall, and the cardiogram showed no regression of right ventricular hypertrophy.

It must be admitted therefore, that at the moment medical treatment directed to opening up the pulmonary vascular bed in this type of congenital heart disease is likely to be ineffective, at least over the age of five years.

The Place of Surgery in the Treatment of Congenital Lesions with Left to Right Intracardiac Shunts and Pulmonary Hypertension

Sufficient has already been said to indicate that, whatever the level of a left to right shunt, patients are in danger of heart failure, and of progressive pulmonary hypertension, which is initially hyperdynamic, subsequently vasoconstrictive and finally obliterative. These dangers occur at different ages; in large ventricular septal defects and patent ductus arteriosus, there is danger from heart failure in the very early days of life if the Eisenmenger reaction has not become established at birth. If it has, secondary irreversible obliterative changes in the pulmonary vascular bed occur, and after the age of five years the situation may be irreversible. In atrial septal defects the dangers come later, usually in early or middle adult life. Abolition of the shunt, while the pulmonary vascular bed is still capable of dilatation, can restore the pulmonary circulation to normal, by cutting off the stimulus to vasoconstriction of high pressure and high flow. This is well shown by the fall in pulmonary artery pressure to normal or near normal in many patients with patent ductus arteriosus, when the duct is tied (Ellis *et al*, 1956).

When pulmonary hypertension is slight and pulmonary blood flow considerable, closure of the ductus carries a very low operative mortality, around 0 5 per cent. When pulmonary hypertension is present, the risks are higher, being very roughly proportional to the severity of the hypertension Ellis *et al.* (1956) have reviewed the reported cases of patent ductus with pulmonary hypertension. Their figures are instructive. When the systolic pulmonary artery pressure was between 40 and 60 mm. Hg, the operative mortality was four per cent; when the pressure was between 60 and 90 mm Hg, the mortality was 19 per cent; and when greater than 90 (that is, near systemic level), it was 31 per cent. Where a right to left shunt was present, the death rate was 56 per cent. There were five deaths in their 30 cases, all in patients with a right to left shunt.

Patients with a right to left shunt are, of course, usually in the Eisenmenger class,

unless the left to right shunt is large and the right to left trivial. Ellis *et al.* (1956) recommend that the response of the hypertension to digital occlusion of the duct at thoracotomy must be assessed in any patient with a patent ductus and pulmonary hypertension. If the pulmonary artery pressure falls, the duct may probably be safely ligated. If the pulmonary pressure rises or is unchanged, and the systemic pressure falls, the duct may probably be safely ligated. If the pulmonary pressure rises or is unchanged, and the systemic pressure falls, the pulmonary flow is not contributing to the hypertension and the ductus is acting as a safety valve and should not be tied.

The dangers of allowing severe progressive vasoconstrictive hypertension to go unchecked are obvious, and it is clear that pulmonary hypertension is an indication for ligation of the ductus, although the risk may be appreciable if the pulmonary artery pressure nearly approaches the systemic. When there is a small right to left shunt, the outlook is more gloomy, but thoracotomy with preliminary manual compression of the ductus is justified. When the left to right shunt is absent, and the right to left appreciable, operation is completely contra-indicated.

In ventricular septal defect the same general principles apply, and closure is now routinely possible with the aid of total cardio-pulmonary by-pass (Warden *et al*, 1957; Kirklin *et al*, 1957; Gerbode *et al.*, 1958, Cleland *et al.*, 1958).

Experience at Hammersmith Hospital indicates that when the pulmonary blood flow is large (pulmonary.systemic flow ratio two to one or more), and the pulmonary arteriolar resistance under seven units, the risks are small Such cases usually have a mean pulmonary artery pressure after closure of the defect of 40 mm. Hg or less, and the post-operative course is apparently largely determined by this assessment, for hypertensive patients who do not have an appreciable fall in pulmonary artery pressure tend to do badly. The pre-operative level of the pulmonary artery pressure alone should not determine operability, for a satisfactory reduction in pulmonary artery pressure, and excellent results have been obtained in patients with systolic pulmonary artery pressures above 70 mm. Hg and even at systemic level. When the resistance is above ten units, however, the hazards are greater, for in such patients organic pulmonary vascular disease is likely to be present, the pulmonary artery pressure may fail to fall sufficiently, and there is a risk of acute right ventricular failure in the immediate post-operative period. The pulmonary arteriolar resistance related to the mortality in 50 cases of ventricular septal defect operated on at Hammersmith Hospital is shown below:

Pulmonary arteriolar resistance (units)	*No. of cases*	*Mortality*
1–8	35	2 (6%)
Over 8	15	4 (25%)
Total	50	6

But the numbers of high-resistance cases are small, and not all the deaths in this group were due solely to right ventricular failure and unrelieved pulmonary hypertension.

Fig. 125 shows the relationship of the pre-operative pulmonary artery pressure, arteriolar resistance, pulmonary artery oxygen saturation, and pulmonary–systemic flow ratio respectively to the ratio of mean pulmonary artery to systemic arterial pressure immediately after closure of the defect. *These figures are not statistically significant* in view of the relatively small numbers and the multiple factors involved. In spite of the

wide scatter, a trend is evident, and the most satisfactory final pressures have occurred in patients with a resistance of less than ten units. The highest mortality has been in the

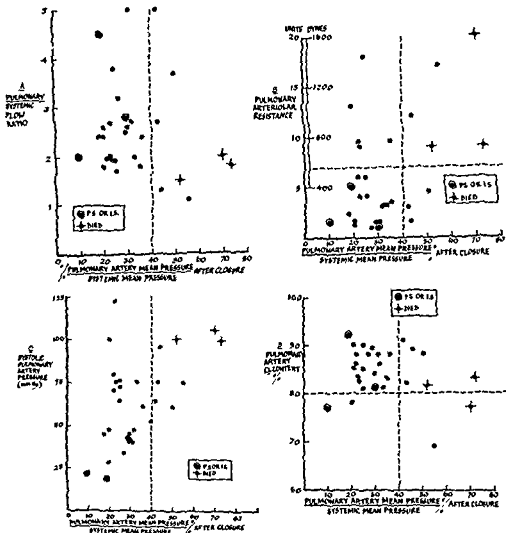


FIG 125 The ratio of mean pulmonary artery pressure to mean systemic pressure immediately after closure of ventricular septal defect in relationship to

(A) Pulmonary systemic flow ratio r = 0 36
(B) Pulmonary arteriolar resistance r = 0 34
(C) Systolic pulmonary artery pressure r = 0·66
(D) Pulmonary artery oxygen saturation r = 0 22

} Measured before operation by cardiac catheterization

Each spot represents one patient
P S = pulmonary stenosis
I S = infundibular stenosis

patients with substantial pulmonary hypertension and high pulmonary resistance who have not shown a satisfactory fall in pulmonary artery pressure after closure of the defect.

The removal of the hyperdynamic and vasoconstrictive influences usually results in

unless the left to right shunt is large and the right to left trivial. Ellis *et al.* (1956) recommend that the response of the hypertension to digital occlusion of the duct at thoracotomy must be assessed in any patient with a patent ductus and pulmonary hypertension. If the pulmonary artery pressure falls, the duct may probably be safely ligated. If the pulmonary pressure rises or is unchanged, and the systemic pressure falls, the duct may probably be safely ligated. If the pulmonary pressure rises or is unchanged, and the systemic pressure falls, the pulmonary flow is not contributing to the hypertension and the ductus is acting as a safety valve and should not be tied.

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ford *et al*, 1957). Straightforward secundum defects may be repaired under hypothermia, but more complex defects and ostium primum lesions require cardio-pulmonary by-pass. Operation should not usually be considered if the left to right shunt is small and balanced by a right to left, the systolic pulmonary artery pressure around 100 mm. Hg, or the pulmonary vascular resistance exceeds five to seven units, for the risks are considerable. A small right to left shunt due to streaming from the inferior vena cava, with a normal pulmonary vascular resistance need occasion no alarm and is in no way a contra-indication to operation.

After operation the triscuspid flow murmur usually disappears, and the pulmonary second sound often moves normally with respiration.

In some cases associated pulmonary stenosis will require resection.

The therapeutic outlook for patients with the Eisenmenger syndrome is, unfortunately, not good. Surgery has nothing to offer, and medical treatment must fall back on the management of heart failure when it occurs, and perhaps on anticoagulants to discourage thrombo-embolic complications Vasodilator drugs appear to be well nigh useless.

It is possible, however, that if the shunt could be abolished in very early life, before secondary changes have fixed the high resistance in the pulmonary vascular bed, patients might be improved Possibly also, drugs might help in reducing the pulmonary resistance in the first year or two of life.

The protective effect of pulmonary stenosis has already been commented upon. Wood (1958b) quotes a patient with an aorto-pulmonary septal defect in which stenosis of the right pulmonary artery was also present. Acetylcholine reduced the pressure in the right lung, but not in the left. He also mentions the observation of McKim and Wiglesworth (1954), that in such a situation the small pulmonary arteries in the side of the stenosis are normal, but show medial hypertrophy in the other lung (Chapter 6, Fig. 66).

These observations lend weight to the suggestion that cure might be achieved if the hypertension could be abolished by closing the shunt very early in life Possibly the creation of pulmonary stenosis in infants under the age of one or two years, preparatory to closing the defect, might be of value (Dammann and Ferencz 1956; Wood 1958b), but the day is fast approaching when closure should be possible soon after birth, using cardiopulmonary by-pass.

THE PULMONARY CIRCULATION IN PATIENTS WITH OTHER ABNORMALITIES OF THE PULMONARY VASCULAR SYSTEM

Pulmonary Arterio-venous Fistulae

Congenital arterio-venous aneurysms of the lung are often multiple, and associated in about 50 per cent of cases with similar aneurysms elsewhere. The effect of the aneurysm in the lung is to shunt blood directly from the pulmonary artery to the pulmonary veins, without opportunity for oxygenation Thus a right to left shunt occurs. The blood flow to normal parts of the lung may be reduced. The clinical picture is one of central cyanosis and clubbing, often multiple telangiectases on the skin (of face and buttocks especially), and a continuous murmur over the affected area of the lung The heart is not enlarged unless the shunts in the lung are very considerable Cardiac catheterization has revealed

a smart fall in pulmonary artery pressure. If the pressure does not fall, then the resistance must rise when the flow is reduced and in such cases it seems probable that pulmonary vasoconstriction actually occurs after closure of the defect. This must obviously place a severe burden on the right ventricle and may explain the higher mortality when the pulmonary pressure is uninfluenced by abolition of the *shunt (Cleland et al., 1958; Bentall et al*, 1959)

From the clinical aspect, the most satisfactory results may be expected from patients *with a full-length septal defect murmur and thrill*, a good apical mid-diastolic murmur, left ventricular but little right ventricular enlargement, and obvious pulmonary plethora (Fig. 118). The cardiogram should show mainly or entirely left ventricular enlargement. Patients with a short systolic murmur and thrill, poor mid-diastolic murmur, and marked right ventricular enlargement with accentuated pulmonary valve closure (Fig 118) are likely to carry a higher operative mortality (Bentall *et al.*, *1959)*, but this may be reduced with further experience.

Where there is appreciable arterial desaturation, and small left to right shunt with *balanced pulmonary and systemic pressures the Eisenmenger reaction has occurred and* operation is of no avail.

After successful operation, the defect murmur usually disappears, but an ejection murmur may remain, probably due to residual infundibular hypertrophy and dilatation of the pulmonary artery (Fig. 118) Reappearance of a long pansystolic murmur suggests breakdown of the septum, but may be due to mitral incompetence

The effects of abolition of a left to right shunt upon the pulmonary vascular system are not yet fully known. In hypertensive patients Heath *et al* (1958) have claimed that the *fall in pressure immediately after closure of the defect is greatest in subjects with only* medial hypertrophy in the small pulmonary arteries, while the hypertension persisted in those with occlusive lesions, indicating that both vasoconstrictive and organic factors operate to influence the result. *Burchell (1959) reported nine patients (five with atrial* septal defect, two with patent ductus, and two with ventricular septal defect) who had been studied before and after closure. In the atrial septal defect patients the pulmonary resistance did not fall after operation, but did fall in one of the two patients with patent ductus, and in both the patients with ventricular septal defect In one of the atrial septal defect patients the calculated resistance actually rose immediately after operation It must be remembered however, that the accurate assessment of resistance is fraught with great difficulty, and in the assessment of pulmonary hypertension attention must also be paid to clinical and cardiographic features which suggest changes in right ventricular and pulmonary pressure. It is safe to predict that the most complete and rapid reduction in pulmonary resistance will occur in patients with the least pulmonary vascular disorder *(Bentall et al 1959). In hypertensive patients the degree and speed of fall in resistance* rem [illegible]
vas [illegible]

fast as a result of new experience. Firm rules should not therefore be [illegible] opinion has crystalized in the light of further knowledge of the problems involved.

In atrial septal defect operation is indicated when the *pulmonary blood flow is around* twice the systemic, as the majority of such patients do not survive past middle age (Bed-

The mitral valve has thickened leaflets and short fused chordae due to abnormal endocardial development. The right ventricle is hypertrophied.

The prognosis is poor, and all but one of the 43 cases reviewed by Ferencz *et al.* died under the age of three years.

The diagnosis is difficult, but may be suspected if sudden attacks of dyspnoea suggesting pulmonary oedema appear between the ages of three months and two years. Cyanosis, sometimes peripheral, but sometimes due to a right to left shunt may be seen, and when this is marked in the lower extremities, a patent ductus with reversed flow is very probable. Unfortunately, the typical mid-diastolic murmur of mitral stenosis is rarely heard, although the first heart sound may be accentuated. A loud systolic murmur may be heard. The cardiogram shows right ventricular hypertrophy, but little evidence of left atrial hypertension. Nor does radiology help, for the left atrium is apparently not usually enlarged, and good evidence of pulmonary venous hypertension may be lacking.

Diagnosis rests upon the history, and upon the presence of a complicated lesion such as co-arctation or patent ductus which is atypical, and upon an unusually marked degree of right ventricular hypertrophy on the cardiogram. An elevated pulmonary capillary "wedge" pressure at catheterization affords strong corroboration.

Treatment consists of mitral valvotomy with closure of an associated ductus (unless the shunt is reversed) and resection of the co-arctation if present.

Mitral atresia. This is usually part of an extensive abnormality of the left side of the heart, such as left ventricular hypoplasia, and aortic atresia, and is not usually compatible with life for more than a short period.

Cor triatriatum. This very rare malformation consists of an extra chamber which lies within the left atrium and receives the pulmonary veins (Keith *et al*, 1958). There is virtually a shelf running across the left atrium, with a small orifice between it and body of the left atrium and the mitral valve.

The haemodynamic picture is that of pulmonary venous hypertension, pulmonary arterial hypertension and right heart failure. the condition mimics mitral stenosis.

Clinically, the features are very similar to those of congenital mitral stenosis, without evidence of associated anomalies. The physical signs are those of pulmonary hypertension, the heart and pulmonary arteries are enlarged radiologically and shadows of pulmonary oedema may be seen. The cardiogram shows gross right ventricular hypertrophy.

According to Keith *et al.* (1958), the diagnosis is certain if at cardiac catheterization the pulmonary wedge pressure is elevated but the left atrial pressure (obtained by passing the catheter through a patent foramen ovale) is low or normal.

Additional anomalies of some pulmonary veins may be present, such as stenosis or drainage into the caval veins or right atrium. The condition is worth diagnosing, for the communication between the accessory chamber and the left atrium proper can be enlarged surgically. The prognosis is governed by the size of this ostium, and if in the region of 1 cm. in diameter, the patient may survive into adult life (Keith *et al*, 1958). Stenosis of the pulmonary veins (probably of congenital origin), at their junction with the normal left atrium has been described by Bernstein *et al* (1959). A marked bronchial circulation developed, leading to haemoptysis, while severe pulmonary vascular disease was also present.

normal intracardiac pressures but a high or normal cardiac output. The hazards to the patient are principally from hypoxia, polycythaemia, and haemorrhage from the aneurysm (Baker and Trounce, 1949). When one or two aneurysms only are present, lobectomy or segmental resection is indicated and should be curative (Le Roux, 1959).

Congenital Absence of One Pulmonary Artery

In this condition the whole of the cardiac output passes through the sole pulmonary artery. The pulmonary artery pressure is normal at rest but may rise on exercise. The lung involved handles about one-half of the total ventilation, but only six per cent of the total oxygen uptake (Madoff *et al.* 1952). Fisher and Van Epps (1959) found no evidence of pulmonary insufficiency in three cases. The lesion is often associated with other congenital cardiac anomalies. (McKim and Wiglesworth, 1954).

LESIONS ASSOCIATED WITH LEFT ATRIAL OR PULMONARY VENOUS OBSTRUCTION

1. *Mitral stenosis.*
2. *Mitral atresia.*
3. *Cor triatriatum.*
4. *Infradiaphragmatic insertion of the pulmonary veins.*

These conditions all cause pulmonary venous hypertension, and the changes in the pulmonary circulation may be accepted as identical with those typified by acquired mitral valve disease (Edwards, 1957) and discussed in Chapter 8. Lesions involving the left ventricle, such as congenital aortic stenosis, co-arctation of the aorta, or fibro-elastosis will not be discussed separately.

Congenital mitral stenosis is an uncommon lesion. Only nine cases were found in 2067 consecutive autopsies at the Montreal Children's Hospital (Ferencz *et al.*, 1954). These authors presented nine of their own cases and reviewed 34 from the literature There were usually associated anomalies (only eight cases having isolated mitral stenosis) especially patent ductus arteriosus, aortic stenosis, and co-arctation of the aorta

The pulmonary circulatory pathology is influenced by the presence of associated lesions. When the latter are absent, pulmonary venous hypertension and the typical pulmonary vascular changes are present. When there is an atrial septal defect allowing a left to right shunt to occur, proximal to the mitral valve, the pressure on the lungs is to some extent relieved, and the characteristic hypertensive changes may not always occur, although the pulmonary blood flow is increased. This is the situation in Lutembacher's syndrome.

When there is a defect distal to the mitral valve (ventricular septal defect or patent ductus), the shunt may be in either direction. If left to right, the lungs are exposed to the effects of pulmonary venous hypertension and to an increased pulmonary blood flow; so that there are two causes for vasoconstrictive pulmonary hypertension. If the pulmonary vascular changes are marked and severe, then the flow through the ductus or septal defect may become reversed (Ferencz *et al*, 1954).

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Infradiaphragmatic total anomalous pulmonary venous connection. This unusual syndrome has recently been reported by Johnson *et al.* (1958), who documented four cases in which all the pulmonary veins drained into a common vein which passed through the diaphragm and entered the porta hepatis. The syndrome is quite different to that of total anomalous pulmonary venous drainage above the diaphragm, for the pulmonary venous return is partially obstructed, and the haemodynamics are therefore those of mitral stenosis, with dyspnoea and cyanosis appearing in the first few days of life.

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not uncommon finding in premature babies dying of asphyxia (Claireaux, 1958; Potter, 1953).

Predisposing Factors

The respiratory distress syndrome, with or without hyaline membrane formation, occurs almost exclusively in three groups of newborn babies; firstly, those born prematurely—and the more immature the higher the incidence of the syndrome (Silverman and Silverman, 1958); secondly, those born by Caesarean section, and, thirdly, babies of diabetic mothers. Only very exceptionally is the hyaline membrane syndrome found except in these circumstances

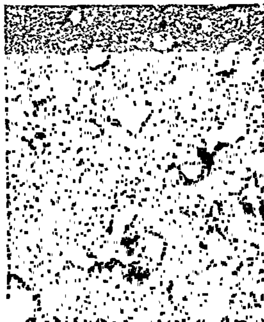


FIG 126 Micro-photograph of the lung showing congestion, collapse of alveoli with distension of alveolar ducts and patchy hyaline membrane formation

Symptomatology

It has frequently been said that the first signs of respiratory distress develop some hours after birth, but closer observation suggests that most, if not all, affected babies are ill from the start (Latham *et al.*, 1955; Rogers *et al.*, 1956; Miller, 1957; Miller *et al.*, 1958, James, 1959). There is frequently apnoea at birth; retractions of the chest wall may be present with the first breaths and persist; respirations may be slow and irregular A temporary systemic hypotension appears to be of significance (Neligan, 1959, Segal *et al*, 1959). An expiratory grunt is frequently heard, with or without a stethoscope, and usually indicates that the baby's condition will worsen

Characteristically, deterioration takes place within 12 hours of birth. Although the respiratory rate is variable, there is usually a significant increase over that observed in the first four hours and often marked tachypnoea.

CHAPTER 10

THE PULMONARY HYALINE MEMBRANE SYNDROME OF THE NEWBORN

By J. P. M. TIZARD

IN England today only about 27 of every 1,000 children born alive die before reaching adolescence, but half of them die in the first week of life. More than half these early neonatal deaths are attributed to respiratory dysfunction, mainly in prematurely born infants The commonest morbid anatomical finding is pulmonary atelectasis and associated with it in about two-thirds of cases are structureless acidophilic staining membranes lining the terminal air passages.

Hyaline membranes in the lungs of newborn infants were described in 1903 and studied extensively by Farber 30 years later (Farber and Sweet, 1931; Farber and Wilson, 1932, 1933). In the past decade many hundreds of papers on the subject have been published, but the pathogenesis and consequences of hyaline membrane formation are still not fully understood.

Nomenclature

Hitherto "hyaline membrane disease" has been a post-mortem diagnosis (but see Osterlund and Hjelt (1959)) The symptomatology and course of the illness are well recognized, but in babies who recover it has not been possible to make the diagnosis with certainty and in some of those who die atelectasis is found without hyaline membrane formation. Moreover, it is not known if hyaline membrane formation is indicative of a single disease process and the role of the membrane in the symptomatology of neonatal respiratory distress is disputed. (Gruenwald (1958) has called it the eosinophilic herring, believing that it distracts attention from the more important atelectasis, but Craig *et al.* (1958) believe that the membrane is obstructive to gaseous exchange.) For all these reasons the term "hyaline membrane disease" has been challenged and the terms "pulmonary syndrome of the newborn" (Bound *et al.*, 1956) and "idiopathic neonatal respiratory distress syndrome" offered as substitutes.

Pathology

The lungs are firm and dark red, oedematous and congested. Histologically the alveoli are collapsed but the alveolar ducts over-distended, indicating secondary or resorptive atelectasis; some primary atelectasis may co-exist Some of the alveoli, alveolar ducts and terminal bronchioles are lined with a thick acidophilic membrane, sometimes, but not always containing cellular debris, but the extent and distribution of this membrane are very variable There is sometimes evidence of intra-alveolar haemorrhage or pneumonia (Fig. 126). The heart is usually dilated. Cerebral intraventricular haemorrhage is a

cases there is usually good correlation with a finding of hyaline membrane, but this is not invariably the case.

Burnard (1959b) has convincingly demonstrated by radiology that the heart is early enlarged in newborn babies with respiratory distress and that its size diminishes as symptoms abate

Laboratory Findings

Blystad (1956) examining "arterialized" capillary blood in a newborn infant with respiratory distress, showed that the oxygen tension and pH were reduced, the carbon dioxide tension raised, but the content normal. These findings have been confirmed and the additional observations of reduced bicarbonate with raised carbon dioxide tension and of increased organic acids demonstrates that respiratory and metabolic acidoses co-exist and suggests that anaerobic metabolism and renal failure may accompany the respiratory dysfunction (Segal *et al.*, 1957, Miller and Smull, 1957; Usher, 1959a; James, 1959) There is a progressive increase in both respiratory and metabolic acidosis in fatal cases. A high serum potassium has also been reported in neonatal respiratory distress (Rose, 1958; Usher, 1959b) and this may reflect a loss of intracellular potassium due to the acidosis (Lynch *et al*, 1956, James, 1959). Osterlund and Hjelt (1959) have found membranes having the same staining properties as hyaline membrane on throat swabs of newborn babies with respiratory distress. If confirmed, this finding will be valuable in permitting diagnosis of the condition in life

Lung Function Studies

It is obviously very difficult to study lung function in seriously ill infants and the published reports are of findings in small numbers of cases Karlberg *et al.* (1954) have shown that the minute volume of respiration is increased due to the rise in respiratory rate, since the tidal volume is normal or reduced (Miller and Smull, 1957). Karlberg *et al* also found that the functional dead space was increased relative to the tidal volume. Cook *et al* (1957) and Drorbaugh *et al.* (1957) have shown that the "vital capacity" (*i e* the volume change between "maximum" expiration and "maximum" inspiration) is lowered. Measurements on excised lungs of fatal cases suggest that the functional residual capacity is reduced (Gribetz *et al.*, 1959) Intraoesophageal pressure differences during respiration are increased (Karlberg *et al.*, 1954) and the lung compliance is markedly reduced in comparison with healthy premature babies (Drorbaugh *et al.*, 1957). These authors have calculated that the work of respiration in ill babies is increased due to the tachypnoea and "stiffness" of the lung from fourfold to tenfold and suggest that death is due to exhaustion

Ventilation perfusion ratio and diffusion have yet to be determined satisfactorily in severely ill babies.

Cardiovascular Studies

The radiological and pathological evidence for cardiac enlargement have already been referred to The heart rate is usually increased early in the disease, but may decrease as the illness progresses. Bonham Carter *et al.* (1956) showed that the mean venous pressure in the umbilical vein below the diaphragm was higher in premature survivors than in

Retraction of sternum, rib spaces and suprasternal notch give the appearance of respiratory obstruction. (Silverman and Andersen (1956) have proposed a method of scoring to aid in the quantitative measurement of retraction and Bauman (1959) has suggested that the "retraction score" may be helpful in estimating prognosis The extent of retraction, however, may well reflect the vigour of the infant as well as the degree of obstruction.) Diaphragmatic and intercostal muscular contractions may appear to be incoordinated, producing a see-saw movement of belly and chest. On auscultation of the chest, breath sounds seem delayed, short and feeble in relation to the respiratory effort. Moist sounds are seldom heard Generalized oedema is common but whether more so than is the case in premature infants without respiratory distress is not certain The liver may enlarge.

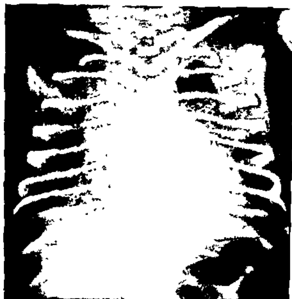


FIG 127 X-ray showing the stage of coalescence of pulmonary opacities with clear bronchial markings

In those babies who further deteriorate, periods of apnoea, sometimes lasting long enough to produce cyanosis, take place, and cyanosis may be constantly present even when respirations are maintained. Sclerema (precadaveric hardening of subcutaneous tissues) is common Fits of various kinds (mainly generalized tonic or focal clonic) may occur. Death usually takes place within 6 to 48 hours. In babies exhibiting the same clinical features who recover, symptoms have usually abated after three days.

Radiology

Donald and Steiner (1953) demonstrated the characteristic radiological appearance of the chest in the hyaline membrane syndrome and their findings have since been confirmed (Peterson and Pendleton, 1955, Ellis and Nadelhaft, 1957; Bauman and Nadelhaft, 1958) Within the first few hours there is generalized fine stippling of the lung fields; later the opacities become coarser and coalesce, the bronchial tree being clearly demarcated (Fig. 127). Recovery may take place in babies showing this radiological appearance; in fatal

Premature babies can survive at lower body temperatures than would be the case in older children or adults The work of Cross *et al* (1958) suggested that the lowered body temperature of the ill newborn baby might reflect a protective reduction of metabolism in response to hypoxia. Maintenance of low body temperature has not proved beneficial in the routine care of babies with respiratory distress (Silverman *et al.*, 1958) but this does not mean that artificial lowering of temperature might never be justified

Promising results have attended recent efforts to correct the metabolic defects consequent upon anoxia by intravenous administration of glucose and bicarbonate (Usher, 1959a) and, in the case of distressed babies of diabetic mothers, by intravenous glucose and sodium chloride solutions (Reardon, 1959) Stahlman (1959) believes that early digitalization may be beneficial. Treatment with vitamin E has recently been tried in an attempt to reduce capillary permeability (Crosse, 1959). Antibiotics are usually given as prophylaxis against pneumonia. Cortisone is reported to have no effect on the incidence of the hyaline membrane syndrome in babies born to diabetic mothers (Haddad *et al.*, 1956)

High humidity in the atmosphere is usually recommended, but there is no advantage to be gained by employing water mists, with or without detergents (Silverman and Andersen, 1956)

Pathogenesis

For many years it was thought that the hyaline membrane resulted from aspiration and subsequent inspiration of amniotic fluid, however, aspiration of amniotic fluid which may occur in cases of foetal distress produces a different pathological appearance and Potter (1952) could not demonstrate hyaline membrane in the lungs of an anencephalic infant who died some hours after the introduction of 80 c c of amniotic fluid into the trachea It is now clear that the membrane is of endogenous origin (Duran-Jorda *et al.*, 1956) and Gitlin and Craig (1956) have convincingly demonstrated that the main component is fibrin Some still consider that aspiration of amniotic fluid, which is rich in thromboplastin, may play an adjuvant role. However, material having the same staining properties as the membrane has been found in the alveolar ducts of an accessory pulmonary lobe isolated from the bronchial tree (Piper and Kleppe, 1958) The hyaline membrane can therefore be regarded as a pulmonary capillary transudate and must arise either from increased pressure in, or permeability of, the pulmonary capillaries.

Several theories have been proposed to account for possible capillary damage Pulmonary hyaline membranes occur in animals as a result of oxygen poisoning but the oxygen tension must be very high and at least the beginning of the respiratory distress syndrome in the newborn may occur without oxygen therapy. Sjostedt and Rooth (1957) have proposed that it is the sudden increase in arterial P_{O_2} following delivery which may damage the capillaries, hence their suggestion of treatment with oxygen-reduced atmospheres. Kloos (1959) supports the view that raised arterial blood P_{CO_2} is the main agent responsible Some pathological studies have suggested that hyaline membranes may be formed by necrosis of the alveolar wall (Bovet–Du Bois, 1951) or of the bronchial epithelium (Ahvenainen, 1947, Tregillus, 1951; Barter, 1959). The explanation for the formation of membranes currently favoured is that they result from raised pulmonary capillary pressure, secondary to left-sided heart failure. The evidence supporting heart failure has already

those dying with respiratory distress. Low systolic blood pressures have been reported by Neligan (1959) and Segal *et al.* (1959). Sisson (1959) has demonstrated a reduction in blood volume in infants with respiratory distress and Sutherland (1959) an increase in leg volume (probably due to oedema) which parallels the severity of the illness.

Electrocardiography provides evidence of left ventricular preponderance (Rose, 1958; Usher, 1959) and electrocardiographic and phonocardiographic studies show a prolongation of mechanical systole (Vallbona *et al.*, 1959). Rudolph *et al.* (1959) have studied circulatory dynamics in the respiratory distress syndrome by cardiac catheterization and angiocardiography The mean pulmonary arterial pressure was lower in infants with severe distress than in those mildly or not affected. They also demonstrated a widely patent ductus arteriosus

Treatment

No satisfactory method is known of artificially expanding atelectatic lung in the newborn nor of removing hyaline membrane. Treatment is therefore directed at mitigating the circulatory, respiratory and metabolic consequences of the condition in the hope that spontaneous re-expansion of the lung and resorption of the membranes will take place.

The indications for oxygen therapy, the concentrations to be administered and the methods of administration are far from clear. Cyanosis is generally accepted as indicating the need for oxygen therapy, but cyanosis is not necessarily a good guide to the degree of hypoxia. For example, the polycythaemia of the newborn may cause cyanosis to become apparent at a relatively small degree of hypoxaemia, but the presence of foetal haemoglobin and lowered body temperatures in displacing the oxygen dissociation curve to the left, have the opposite effect, and a premature baby might be in need of added oxygen even when pink. There are considerable difficulties in the estimation of arterial blood gas tensions as a routine procedure in premature babies. The extent to which hyperpnoea and restlessness indicate hypoxia has yet to be determined. The growing suspicion that the hyaline membrane syndrome is related to anoxia at birth may also indicate the need for early administration of oxygen.

[illegible] inducing blindness [illegible] widely advocated [illegible] n cause retrolental fibroplasia if the arterial P_{O_2} is low and there can therefore be no objection to a high concentration of oxygen if the baby is cyanosed. In practice, however, there is the difficulty of adjusting the oxygen concentration in the baby showing intermittent apnoea and cyanosis It is also possible that, as in adult chronic bronchitics, a high arterial P_{CO_2} in the baby may result in hypoxia providing the main respiratory drive, and increasing oxygen concentration may depress respiration. To overcome this difficulty and to increase elimination of carbon dioxide attempts at artificial respiration may be justified (Donald, 1954)

In the belief that administration of oxygen may cause hyaline membrane formation (as in O_2 poisoning; see below), Sjöstedt and Rooth (1957) have advocated atmospheres of lowered oxygen content (15 per cent) in the treatment of premature babies

It seems reasonable to limit as far as possible the infant's oxygen needs. Unnecessary handling should be avoided, as this produces active movements and mass reflexes.

and to a certain extent clinically—to the hyaline membrane syndrome of human infants It is known that a newborn infant may receive a large additional supply of blood from the placenta if the umbilical cord is not tied immediately after delivery (Gunther, 1957). However, Taylor *et al* (1959) have shown that delayed clamping of the umbilical cord in premature infants is associated with a *higher* incidence of respiratory distress and a higher death rate; this supports the view that overloading of the circulation may conduce to cardiac failure

Even if it is accepted that left-sided cardiac failure consequent on hypoxia provides the most reasonable explanation for the formation of hyaline membranes in the newborn, many problems remain unsolved It is not clear if the formation of membranes precedes atelectasis or the reverse and the exact sequence of events in respiratory and cardiac disturbance and their metabolic consequences have yet to be elucidated

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been outlined. The finding of low right atrial pressures (Rudolph *et al.*, 1959) is not necessarily opposed to the concept of heart failure, as it may reflect a general circulatory collapse in the very ill infants. Also, James (1959) points out that increased intrathoracic negative pressure due to respiratory distress must be taken into account in interpreting the findings of the relatively low umbilical venous pressures reported by Bonham Carter *et al.* (1956). Cross *et al.* (1959) have shown that in the newborn lamb output of the left heart does not increase with hypoxia and this suggests that heart failure is likely to be the consequence of additional demands brought about by hypoxia. Dawes *et al.* (1955) have demonstrated flows across the ductus arteriosus in newborn lambs and this has been confirmed in human newborn infants (James and Rowe, 1957; Adams and Lind, 1955). Burnard (1959a) has described the quiet crescendo systolic murmur in newborn babies, more commonly heard in those who have suffered hypoxia at birth. Eldridge and Hultgren (1957) have shown lower arterial oxygen tension in the lower than in the upper limbs in hypoxic newborn babies, suggesting that reversion to the foetal pattern of circulation may take place. However, with flow in either direction additional strain would be thrown upon the left heart The pulmonary venous and capillary pressures would rise and result in pulmonary oedema and formation of membranes.

As stated above, closer observation has lead to the conclusion that infants who die with the hyaline membrane syndrome show evidence of respiratory dysfunction at birth. Among premature infants the incidence of hyaline membrane disease is highest in those who have had signs of severe asphyxia at birth and lowest in those who have appeared well (Crosse, 1957). In premature infants delayed pulmonary expansion may be due to immaturity of lung structure (Klemola, 1937; Potter, 1957), higher surface tension of lining layers in the lung (Avery and Mead, 1959) and softness of the thoracic wall. In infants born by Caesarean section slowness in initiating respiration may result from maternal anaesthesia, and other factors connected with abdominal delivery. But the association of hyaline membrane disease with Caesarean section may be due to the complication of pregnancy for which the section was performed, and Weintraub *et al.* (1959) have shown that the hyaline membrane syndrome following Caesarean section is strongly associated with a placenta praevia or other bleeding complications of pregnancy. Infants of diabetic mothers who develop symptoms of neonatal respiratory distress may show disturbances in the initiation of respiration, and Hsia (1959) states that foetal mortality in babies of diabetic mothers is related to their condition at birth Babies born to diabetic mothers show similar biochemical disturbances to those which characterize respiratory distress in the premature infant (Reardon, 1959)

One other theory of the causation of the respiratory distress syndrome must be mentioned. Jäykkä (1954) in experiments on excised lungs, suggested that erection of lung capillaries following circulatory adjustments at birth played an important role in promoting expansion of the lung. The subsequent work of Avery and colleagues (1959) indicates that [illegible] but [illegible] ight [illegible] 957). This view was supported by the observations of Mahaffey and Rossdale [illegible] newborn foals who, when born indoors under human supervision and possibly deprived of placental blood by early tying of the cord, developed an illness similar pathologically—

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EMPHYSEMA HEART

Before the present century the association of pulmonary arterial thickening with intrinsic disease of the lungs was recognized by Senac (1749), Louis (1835), Budd (1840) (quoted by Samuelsson, 1950), and also by Laennec, Bouillaud and Dittrich (quoted by Taquini, 1954). The occurrence of right heart hypertrophy in these conditions was also appreciated and regarded as a consequence of elevated pressure in the lung vascular bed. Little progress was made, however, beyond simple morbid anatomical observation, and in the first quarter of this century the clinical study of heart failure in chronic lung disease passed through a period of relative neglect The bronchitic invalid with few physical signs of interest to the students of the time, and regarded as a "chronic", was often relegated to the then less well-equipped municipal hospital Teaching hospitals thus had little experience of the disorder. White and Jones (1928) found that cor pulmonale occurred in less than one per cent of 2341 instances of organic heart disease admitted to the Massachusetts General Hospital To the cardiologists the heart was so well concealed under the over-expanded lungs that it could neither be heard nor felt satisfactorily, and even its radiology (Parkinson and Hoyle, 1937) and electrocardiography were often unilluminating Furthermore, in the Mackenzie-Lewis era of British cardiology, consideration of failure affecting one side of the heart more than another was somewhat discouraged.

Incidence and Aetiological Factors

It is difficult to assess the exact frequency of pulmonary heart disease in the population, as most of the figures are based on hospital statistics which are notoriously fallacious as population samples In the autopsy data from Hammersmith Hospital (1935–50) 114 out of 4700 cases (2·4 per cent) had right heart hypertrophy as the major lesion, and 109 of these had chronic bronchitis In Belfast McKeown (1952) found 111 instances of chronic cor pulmonale (1·6 per cent) in 6770 autopsies. Flint (1954) found that 75 out of 500 patients with heart failure admitted in one year to one hospital in Sheffield were suffering from chronic cor pulmonale In all the published series there is a strong proponderance of males ranging from 75 per cent upwards Chronic bronchitis, the major aetiological factor, is rare before the fourth decade, reaches its maximum by the sixth decade and declines in frequency thereafter Cor pulmonale below the age of 40 is not likely to be due to bronchitis Bronchiectasis, tuberculosis and rarer disorders of the lung vessels should be considered when signs of cor pulmonale develop in young adults. Bronchitis has a higher frequency in the lower social classes, where crowding with increased liability to respiratory infection and exposure to inclemencies of weather in occupation may play a part. Dusty occupations and smoking may play some part also

The rôle of asthma in the production of emphysema and cor pulmonale has been overestimated in the past Most clinicians now believe that asthma *per se* is only a minor aetiological factor in emphysema, though it is well known that asthma often accompanies chronic bronchitis. Orie and his associates in Groningen have emphasized the occurrence of eosinophils in the sputum and asthma in the families of many cases, but Stuart-Harris and Hanley (1957) discount sputum eosinophils under 20 per cent as evidence for asthma. In the rare instances of fatal asthma, however, cor pulmonale is often recognized patho-

CHAPTER 11

CHRONIC PULMONARY HEART DISEASE (CHRONIC COR PULMONALE)

BY JOHN McMICHAEL

COR pulmonale may be defined as that group of cardiac disorders developing as a result of obstruction of the flow of blood through the lung alveoli from (1) parenchymal disease of the lung or abnormality of the thoracic cage, or (2) from disorders arising primarily in the pulmonary vascular bed.

Aetiology of Chronic Pulmonary Heart Disease

A Parenchymal disorders of the lung:

1. Emphysema due to bronchitis with or without asthma.
2. Fibrotic changes with or without emphysema:
    - Tuberculosis.
    - Pneumonoconioses
    - Sarcoidosis
    - Scleroderma lung.
    - Radiation fibrosis.
    - Lymphangitis carcinomatosa.

B Alterations in the thoracic cage.

1. Kyphoscoliosis.
2. Thoracoplasty
3. Extreme obesity.

C. Disorders of the pulmonary vessels:

1. Recurrent pulmonary embolism.
2. Thrombosis of the pulmonary artery.
3. Tumour embolism (chorionepithelioma).
4. Bilharziasis.
5. Sickle-celled anaemia.
6. Pulmonary polyarteritis.
7. Rheumatic arteritis.
8. Idiopathic pulmonary hypertension.

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logically and this may account for a higher documentation of asthma as a causal factor in autopsied than in clinical series (McKeown, 1952; Spain and Handler, 1946).

Pathology and Pathogenesis of Emphysema Heart

In patients dying of clinically recognized emphysema, the heart usually shows an obvious hypertrophy of the right ventricle with increased thickness of its wall, but sometimes dilatation may conceal the increase in thickness. There may also be evidence of dilatation of the tricuspid ring when tricuspid valvular incompetence has developed in the later stages of the disorder. In 30 per cent of cases there may be some enlargement of the left ventricle as well as the right, for systemic hypertension is a not infrequent accompaniment in the age group affected by emphysema.

The large pulmonary arteries show dilatation and atheromatous plaques, though these are usually moderate in extent and seldom advance to the point of ulceration and calcification. The finer pulmonary artery branches may show a little hyaline thickening comparable to the condition of the peripheral arteries in systemic hypertension.

The pathology and pathological physiology of the emphysematous lungs are discussed in Chapter 6

The manner in which these anatomic disturbances in the lungs and the functional alterations of their ventilation impede the lung circulation has been subjected to much investigation in recent years. Two factors are involved: an obliterative and a functional obstruction to pulmonary blood flow.

The obliterative factor. It was natural that destruction of the alveolar capillaries, a demonstrable and visible lesion, should have historical priority among the hypotheses of pulmonary hypertension Direct measurements of pulmonary blood flow and vascular pressures, however, have put the problem in a new light. The following facts have emerged:

1. The normal lungs can accommodate at least a doubling of cardiac output without any significant increment of pulmonary arterial pressure. In left to right cardiac shunts such as atrial or ventricular septal defect minute volume up to four times the normal may occasion no rise in pulmonary pressure The lung vascular bed normally presents a very low resistance and a large distensible capacity.
2. Removal of one lung does not increase the pulmonary arterial pressure. Denolin (1955) notes that under these circumstances the pulmonary circulation time is not shortened in spite of the doubled blood flow through the remaining lung Thus the capacity of the vessels of the remaining lung must also be doubled.
3. It follows that the vascular network of the lung must be very grossly reduced if it is to contribute to pulmonary hypertension. Capillary loss probably plays less part than the accompanying severe narrowing and atrophy of pulmonary arterial branches demonstrated in emphysematous lungs in life by angiographic studies (Bolt *et al.*, 1957)
4. As emphysema becomes advanced this anatomical factor becomes increasingly important and it is probably responsible for both the elevation of pulmonary arterial pressure which persists between attackes of bronchitis and a rising pressure when these subjects take exercise (Hickam and Cargill, 1948)

The functional factor. When an emphysematous subject develops venous congestion and dependent oedema he will almost invariably be suffering from an exacerbation of his

bronchitis with increased cyanosis. Bloomfield *et al* (1946) noted that the pulmonary arterial pressure rose higher with the onset of heart failure in emphysema and Mounsey *et al.* (1952a) showed in a series of cases an acute rise of pulmonary arterial pressure with the asphyxiating attack of bronchitis and recovery towards normal with improved ventilation as the attack subsided. Taquini *et al* (1949) showed that the heart, dilated in the acute exacerbations of chronic bronchitis, recovered practically to normal volume between attacks. This condition he called "subacute bronchogenic cor pulmonale"

This functional and recoverable pulmonary hypertension is of great importance. It seems to be related to plugging of small bronchi with mucopurulent exudate, and it is independent of the amount of alveolar destruction for there are rare instances of recurrent bronchiolitis with asphyxia and episodes of pulmonary hypertension in whom there is no demonstrable loss of alveolar walls (Clinico-Pathological Conference, 1951). In these circumstances high pulmonary pressure is functional rather than structural The precise manner of development of this pulmonary hypertension in an asphyxiating episode of bronchitis is obscure but its reversible character is responsible for the quite remarkable recovery from failure, which can vanish nearly completely between bronchitic episodes

The Sheffield investigators (Davies, 1951; Stuart-Harris and Hanley, 1957) showed that the renal circulation, depressed in attacks of congestive failure in chronic bronchitis, recovered remarkably between attacks, and in this respect emphysema heart failure differed from mitral stenosis where little renal circulatory improvement took place even when a dropsical patient was rendered oedema-free

It was thought that alveolar hypoxia constricted the pulmonary arterioles, as such a reaction had indeed been demonstrated in certain types of physiological experiment in animals and man (Euler and Liljestrand, 1946, Motley *et al*, 1947, Dirken and Heemstra, 1948) This reaction seemed to provide an attractive explanation for the pulmonary vasoconstriction of the bronchitic exacerbation, as such attacks further depress the arterial oxygen saturation Unfortunately, oxygen administration with restoration of full saturation of the blood leaving the lungs does not always reduce the pulmonary arterial pressure Boake *et al* (1959) suggest that the passage of blood with a low oxygen content into the alveolar capillaries raises the pulmonary vascular resistance such an explanation leaves the absence of pulmonary hypertension in cyanotic congenital heart disease unexplained Yu *et al* (1953) in Rochester found that pulmonary hypertension was more closely correlated with a rising arterial CO_2 *than with falling arterial oxygen Rossier et al. (1956) in* Zurich noted that pulmonary vasoconstriction occurred when bronchial passages were blocked and thus emphasized alveolar hypoventilation rather than altered alveolar gas tensions as a probable initiating factor It was shown by McMichael and Sharpey Schafer (1944) that the patient in emphysema heart failure often had a well-sustained or even high cardiac output This is partly a response to hypoxia and partly a consequence of the increased metabolism of the breathless patient, often with a slight elevation of body temperature Mounsey *et al.* (1952a) demonstrated that the elevated output did not account for the elevation of pulmonary pressure.

Shunts between the bronchial and pulmonary circulations have been well demonstrated, especially in bronchiectasis They are less obvious in bronchitis, but their possible function in pulmonary hypertension is often suggested It seems unlikely that they contribute to this development as they are small in magnitude compared with a patent ductus, the

increased flow from which can usually be accommodated in the lung vascular bed without pressure rise.

Increased blood volume in the cyanotic cardiac patient has also been credited with a rôle in the production of pulmonary hypertension. Most measurements of blood volume in these circumstances show a modest increase, and unless it is assumed that the extra blood is entirely located in the lung blood vessels it is difficult to imagine how a small (ten per cent) increase in volume of the total circulating blood could play any part (Stuart-Harris and Hanley, 1957).

All that can be said therefore is that poor air entry into lobules or segments of the lung is often accompanied by pulmonary vasoconstriction. The manner in which this reaction takes place is still the subject of debate (Chapters 2 and 4). In Chapter 12 it is made clear that, in emphysema, the blood flow is not automatically reduced in the poorly ventilated parts of the lung· if it were there would be no cyanosis. It seems possible that bronchial blockage may be more important than mere reduction of oxygen tension, and the hypothesis of Rossier appears to fit the facts. The mechanism however remains to be elucidated and it is possible that autonomic nervous and adrenal reactions may be involved.

Clinical Picture

The onset of emphysema heart failure practically always takes place in an exacerbation of bronchitis, which has been recurrent for many years with increasing disablement in recent attacks. The breakdown is heralded by further cough and sputum and it may even seem to develop after a common cold In England most of these patients are admitted to hospital during the winter months, especially during the coldest months from January to March. In London, fog, and especially acrid smoky fog, has a notorious reputation for precipitation of recurrences and ultimately final circulatory breakdown among the chronic bronchitic population.

The manifestations of active bronchitis are clear. Temperature is seldom above 100°F. in the bronchitic adult. Episodes of coughing with expectoration of yellow and infected purulent or mucopurulent sputum disturb the otherwise breathless, dusky and often drowsy patient The chest, usually but not invariably barrel-shaped, moves poorly, and in addition to the usual rhonchi and râles there is nearly always indrawing of the lower intercostal spaces with relative silence on listening with the stethoscope over these lower lung zones The air passages to these areas are obviously blocked with muco-pus, though air may be heard to enter when the patient makes a maximal inspiratory effort. Occasionally these areas show up in a radiograph as areas of collapse, but usually, in spite of this auscultatory silence, the lungs are translucent Air entry and respiratory exchange are thus impaired with partial lobular collapse only.

The patient prefers to be propped up in bed, as this permits the most advantageous function of his respiratory musculature; it also relieves venous distension in the head on lying flat. Nevertheless he can lie flat for short periods, if required, and, unless there is superadded asthma, he is not subject to attacks of orthopnoea. The facies is often characteristic, with a dusky flush, bluish lips and mucous membranes, including congested conjunctivae. Cheeks and lips are puffed out at each short breath. According to the severity of the condition, the patient's mental state is clouded In severe instances he is

drowsy, or mentally muddled and confused On the other hand, the condition resembles that of drunkenness in that the patient can pull himself together to answer commands or peremptory questions though he relapses quickly into incoherence. Oxygen tents can reduce a talking patient to an unconscious patient. These mental changes are attributable to CO_2 narcosis. The respiratory centre, reduced in sensitivity, seems to be dependent on oxygen lack for its activity When this stimulus is removed by oxygen administration, respiration is depressed, CO_2 tension increases in the blood and unconsciousness results.

In certain patients with severe mental disturbance and associated hypercapnia, examination of the fundus oculi will show congestion of the retinal veins, which may even proceed to the stage of papilloedema with haemorrhages This condition is associated with an elevated cerebrospinal fluid pressure as measured on lumbar puncture, and it has been thought to be related to an increased cerebral vaso-dilatation, produced by the elevated CO_2 content of the arterial blood (Simpson, 1948).

Dependent oedema to a greater or less degree is the usual indication that emphysema has become complicated by heart failure The veins of the neck are engorged and pulsations are visible above the normal limits· in the recumbent position venous pulsations at the level of the manubrium are probably abnormal as the sternum is thrown forward in the barrel chest When the venous pressure rises very high, pulsation synchronous with ventricular systole may be detected, indicating tricuspid insufficiency At this stage the patient may complain of epigastric discomfort due to the engorged liver in which pulsations may be felt when the tricuspid leak becomes considerable

The pulse is usually full and bounding and the rhythm regular. Atrial fibrillation develops in only about ten per cent of cases. The hands are warm, as might be expected in the high output state which is usually found in the earlier stages of emphysema. Arterial blood pressure is usually normal, but on occasions it may be elevated. Howarth *et al.* (1947) noted a correlation of systolic arterial pressure with cardiac output in emphysema heart failure. In some instances the arterial hypertension seems to be a reaction to asphyxia, as it returns to normal when the bronchitic attack is over. In the later stages, when tricuspid incompetence has made its appearance and the patient has entered the terminal stages of the illness, the blood pressure falls along with the fall in minute output which is a necessary accompaniment of tricuspid incompetence.

Fully developed clubbing of the fingers is seldom seen unless the patient has bronchiectasis, although some "parrot bill" curvature of the nails is not uncommon

Examination of the heart itself is made difficult by the thickness of the overlying layer of lung which abolishes any detectable area of cardiac dullness The apex beat may be impalpable and cardiac pulsation is best felt in the epigastrium Auscultation is also better carried out in this situation and, according to circumstances, a gallop rhythm, which may be either presystolic, protodiastolic, or of summation type, may be heard. A systolic murmur also develops when there is tricuspid incompetence

Special Investigations

Radiologically the heart often shows a distinct forward bulge of the outflow tract of the right ventricle, while an postero-anterior chest film shows widening of the heart shadow with a slight upward tilt at the apex due to the enlargement of the right ventricle.

Although the major pulmonary vessels may be enlarged at the root of the lungs this contrasts with the clearer periphery of the lung fields, where blood vessels are usually less prominent than normal. Segmental collapse of the lungs is occasionally seen, but this is not a usual finding, even in the presence of bronchial blockage.

The electrocardiogram is often somewhat disappointing, although the changes are in a direction of right heart hyperthrophy Where the rhythm is normal the P-wave is often peaked, indicative of some strain on the right atrium. Praecordial chest leads show clockwise rotation of the heart, the left ventricular pattern appearing further to the left than usual, and, according to the severity of the condition, one may see either little abnormality in the QRS pattern or a marked R-wave in VR, or variable sized rudimentary or larger secondary R-wave in V1 or V4R, and in more advanced cases, a pattern of incomplete right bundle branch block (Mounsey *et al.*, 1952b) (Chapter 7).

Although a striking diminution in cardiac size may occur with recovery from the attack of bronchitis, the electrocardiographic changes are not usually reversible, and there is only a very approximate correlation between electrocardiographic changes and the severity of the disorder some electrocardiographic abnormality may be found before heart failure has appeared.

The Blood Picture

There has been considerable debate about the occurrence of polycythaemia in patients with emphysema heart. Although in individual cases the haemoglobin concentration and haematocrits have usually been within normal limits, statistically they are significantly above the normal range. The mean haematocrit value is usually a little over 50 per cent and the haemoglobin concentration lies between 17 and 18 g./100 ml.

Numerous studies suggest that the blood volume is increased in emphysema heart failure. The increase, however, is small and it is no greater than might be expected in other instances of congestive cardiac failure.

Blood Chemistry

The arterial oxygen content in an episode of emphysema heart failure is reduced from the normal 95 per cent saturation to values in the region of 60 to 70 per cent though levels as low as 30 per cent saturation are on record. This reduced oxygen content is accompanied by an increased CO_2 tension with an elevation of the serum bicarbonate to values of 30 to 40 m.eq./litre. Along with the rise in bicarbonate, there is a corresponding fall in plasma chloride. The P_{CO_2} rises from the normal 35 to 40 mm. Hg to an average figure of 64 mm Hg, but the pH of the blood is seldom reduced below 7·3.

Prognosis

Once emphysema heart failure has made its appearance the outlook is poor. A quarter of the patients die in their first attack, but a small fraction may get through four of five episodes and survive as long as three or four years after the onset.

Treatment

Anti-infective measures. The first objective is control of the bronchial infection. The organisms most commonly involved are *Strep. pneumoniae* and *Haemophilus influenzae*;

other organisms are found less frequently and are of less significance The virus of the common cold, the adenoviruses, and even the influenza virus may be important precipitating factors. Bacterial invasion may in fact be secondary to primary viral damage in many cases The complex nature of the infective process militates against dramatic success from the use of antibiotics, but nevertheless the wise choice and effective use of suitable combinations of these drugs may be lifesaving. Treatment is begun as a matter of urgency pending a laboratory report of antibiotic sensitivity of the sputum organisms. Penicillin and streptomycin cover a wide range of Gram positive and Gram negative organisms respectively and this combination may be used Chloramphenicol is effective against *H influenzae* and its use is fully justified in seriously ill patients. The broad spectrum antibiotics, such as tetracycline and erythromycin are also often effective. Aerosol inhalations have been suggested, but there is little evidence to suggest that they do any good; it seems very unlikely that inhaled aerosols could penetrate the mucopurulent plugs which block the respiratory passages

Improvement of lung ventilation. Adequate control of the bronchitic exacerbation is the major step in producing the improved ventilation of the lungs which in turn can lead to dramatic amelioration of the circulatory state While waiting for subsidence of the inflammation, every effort should be made to improve lung ventilation: Ephedrine (½ to 1 grain orally three times a day) is often effective. Choline theophyllinate is less irritating to the alimentary tract than aminophyllin, which must usually be given intravenously to avoid gastric irritation. A sublingual tablet of isoprenaline (10 to 20 mg.) is probably better than the inhalation of a spray Even a slight gain in ease of air entry following these "antispasmodic" remedies may be of great assistance, and where bronchitis is complicated by asthmatic wheezing their administration is the more imperative. There is unfortunately less sanction for the use of steroids in the asthmatic bronchitic. Clinical trials have shown that they are of little benefit (Felix-Davies and Westlake, 1956) and of course they may be damaging in the presence of infection. Nevertheless there may be instances in which the benefit may exceed the harm (Bickerman *et al.*, 1955)

Management of Hypoxia. Respiration is normally regulated by centres in the medulla which are stimulated by CO_2 but which are depressed by oxygen lack. The increase in respiration from oxygen lack is initiated in the carotid sinus region especially by receptors in the carotid body In cyanotic emphysematous patients the medullary centres are depressed and unresponsive to CO_2 (Donald and Christie, 1949), the main stimulus maintaining respiration being oxygen lack acting in the carotid body region. Morphine depresses this perilously balanced medullary respiratory mechanism still further and the usual therapeutic doses of this drug can be lethal in emphysema or similarly asphyxiated kyphoscoliotics (Daley, 1945) While morphine, heroin and codeine are especially harmful and should never be used as cough suppressants, other hypnotics are only slightly less dangerous and should be used with great caution and in small doses. On no account should morphine be used in preparation for such investigations as bronchoscopy. The kyphoscoliotic, poliomyelitic cripple who has broken a limb in a fall should only be given morphine under strict consideration of the possible risks.

Even the administration of oxygen may deprive the respiratory centre of a necessary stimulus, as mentioned above, and result in unconsciousness. Oxygen must therefore be given with due caution, and it is important that the patient's reaction be carefully

watched. Some recommend that the oxygen mask should be removed for ten minutes ever hour, while others have found the less efficient methods of oxygen administration of valu for example nasal catheters or Tudor Edwards spectacle frame. There is no rule excep to regulate oxygen therapy according to the needs and reaction of the individual patien The sensitivity of the respiratory centre may be increased by giving sodium salicylat 2 g. four-hourly by mouth (Wegria *et al.*, 1955) and by intravenous nikethamide in doses o 10 ml. Though the action of the latter is short lasting, repetition every two or three hour in the gravely asphyxiated patient may be lifesaving

Management of congestive failure. The episode of failure will improve if the patien recovers from his bronchitis, whatever drugs may or may not be given. Clinical response to various cardiotonic and other measures are thus difficult to evaluate It was observe that the elevated or high normal cardiac output shows little improvement with digitali (Howarth, McMichael and Sharpey-Schafer, 1947) but that when a later stage is reache with falling output and falling arterial pressure some improvement may be achieved Venesection was less likely to produce improvement in the minute output at any stage o the disorder. Some recommend venesection to reduce blood viscosity, while others regar this as needless interference with an important compensating polycythaemia

While the administration of digitalis glycosides in emphysema heart failure may produc little effect on the minute output of the heart, more precise analysis may show an increas in the pulse pressure in the right ventricle, and, if there has been slowing of rate, an in- [illegible] dramatic [illegible] ver. [illegible] y to strengthen the heart's contraction should this become weak. In emergency the most rapid action is obtained by intravenous ouabain (0 5 to 0·75 mg.), and this drug should be used if the patient has reached a stage of circulatory collapse with a falling blood pressure. Ouabain cannot be given orally owing to poor absorption. Where it is thought desirable to maintain digitalization, digoxin 0·25 mg. twice or thrice daily, or pil dig fol. 60 mg may be used.

Cardiac oedema is treated in the same way as in other cardiac disorders. Mercurial diuretics were the most effective agents until recently. Simultaneous ammonium chloride administration, however, should be avoided as this can increase the acidosis already present. For this reason some of the newer diuretics are more advantageous. Chlorothiazide or one of its derivatives is most effective and it can be given by mouth in doses of 0·5 to 1·5 g If used at intervals of three days or more electrolyte balance will readjust itself between doses, but where chlorothiazide is needed every second day for any prolonged period potassium supplements are necessary to avoid potassium depletion. Potassium chloride or citrate in a flavoured mixture should be given in divided doses totalling 4 to 6 g. each diuretic day.

Acetazolamide, by promoting the excretion of bicarbonate in the urine, produces a lowering of the elevated plasma bicarbonate This partial biochemical "correction" has, however, little advantage for the patient, as it leaves the carbonic acidosis unaltered, and the diuretic action of the drug rapidly diminishes when available plasma bicarbonate is depleted.

There have been claims that acetazolamide increases the pH and reduces blood CO_2

tension towards normal, but only after a prolonged period (days or weeks) of administration (Nadell, 1953). As lowering of CO_2 tension can only result from improvement in ventilation of the lungs, this must have occurred during the period of treatment and it seems doubtful if increased pulmonary ventilation is a direct consequence of administration of a diuretic. Certain haemodynamic improvements can occur from diuresis in heart failure (Pugh and Wyndham, 1949) and these may be responsible for a fall in pulmonary arterial pressure which is claimed to follow intravenous injection of acetazolamide (Broustet, 1958) Whatever the immediate pharmacological actions of acute administration of acetazolamide may be, experience in this country has not given any satisfaction with the results of longer term administration (Stuart-Harris and Hanley, 1957).

Sodium restriction is widely recommended in the treatment of heart failure with oedema. Some introduce it with the earliest manifestations while others hold it in reserve till oedema becomes intractable by other methods. Temporary sodium restriction is readily achieved by a "rice-diet" and this may be used if necessary in the acute phase of emphysema heart failure. Should heart failure become chronic severe sodium restriction may be called for when oedema cannot be relieved in any other way· the restriction may be taken through the phases of "no added salt", "no salt in cooking", and finally the prescription of sodium-free foods, especially bread

An undeservedly forgotten method of reducing oedema is that based on Southey's tubes The latter are no longer necessary but the same result may be achieved as follows. The legs are allowed to hang down over the lowered foot end of a Leavis cardiac bed until sufficient oedema has accumulated to make the skin tense The skin is then scarified with multiple superficial incisions made by the light use of a scalpel These cuts need not draw blood. Fluid then drains from the dependent legs and is directed by mackintosh sheets into a receiver on the floor The patient's weight may be reduced by several pounds a day by this method.

In certain chronic cardiac cripples induction of myxoedema has been used to depress metabolic needs Thyroidectomy, thiouracil, neomercazole and radio-iodine have all been used for this prupose. This method is seldom used nowadays.

Resuscitation (see Chapter 12) Patients may be admitted to hospital in severe asphyxia due to an extreme degree of bronchial plugging Blue, collapsed, and apparently moribund, the patient may still be revived. Recoveries have been achieved even with all the signs of imminent death, including dropped jaw, sternomastoid breathing, low blood pressure, leaden cyanosis and subnormal temperature The measures to be applied are as follows. artificial respiration with an immediate intravenous injection of nikethamide (1 gm. or more) and 0·75 mg ouabain. Immediate tracheostomy with the application of bronchial suction to clear the major air passages and the maintenance of ventilation thereafter by means of one of the methods of assisted respiration. If the patient can tolerate a breathing machine he may trigger a positive pressure respirator by his own otherwise feeble inspiratory efforts. By this time other measures outlined above will be applied, and recovery, at least for a time, may be achieved Naturally the patient whose disorder has precipitated such a dire emergency is unlikely to live more than a few months at most before the underlying disorder reaches a final and fatal stage.

Prophylaxis. The prevention of chronic bronchitis is a major challenge to our profession. The complexity of its organismal causes has already been touched on. The rôle

of ageing processes in the lung has still to be evaluated. Environmental and occupational factors include fog-ridden areas (Reid and Fairbairn, 1958) and exposure to cold and wet Cigarette smoking and childhood asthma may also play a rôle in fostering bronchial infection. The young bronchitic may be persuaded to change from an outdoor to an indoor occupation, or to leave a foggy or smoky city. Attacks of bronchitis call for prompt treatment. Efforts have been made to reduce frequency and severity of bronchitic attacks by short courses of antibiotics at the onset of a cold, but without significant success (Knox *et al.*, 1955). Buchanan *et al.* (1958) have given 250 mg. tetracycline twice daily and continuously with an encouraging diminution in the frequency of bronchitic exacerbations. More trials of this type are required before any final conclusions are reached.

Differential Diagnosis of Cor Pulmonale

Where there is some causative lung disorder the recognition of pulmonary heart failure creates little difficulty as a rule. In sarcoidosis, fibroid tuberculosis, and radiation fibrosis (usually from mammary cancer or regional sacroma in the thoracic area) the general features are much the same as in emphysema heart, except that the features are more likely to be unremitting and progress is continuously downhill The same relentless progression of cardiac failure applies to kyphoscoliosis where, owing to ageing processes in the lung, ventilation becomes less efficient and cyanosis becomes increasingly apparent in middle life The pulmonary arterial pressure becomes elevated as the subject gets bluer and cor pulmonale terminates the picture. More recently appreciated is the syndrome of defective ventilation resulting from extreme obesity (Pickwick syndrome). Impaired movement of the chest wall held in its heavy cuirasse of thick fat leads to cyanosis and ultimately heart failure Both right and left ventricles may be enlarged and hypertrophied. Silicosis and anthraco-silicosis are occupational hazards and occur mainly in particular geographical (mining, quarrying) areas. Cor pulmonale is most likely to develop in the advanced stage of massive and confluent shadowing.

Pulmonary bilharziasis is seen to a greater extent in Egypt than in other tropical or subtropical countries. The ova, whose normal mode of exit is by erosion from the veins of bladder or rectum through the mucosa of these viscera, are instead swept away in the blood stream to embolize the portal radicles in the liver (from the rectum) and the pul-

the systemic circulation. In Egypt, where the majority (80 per cent) of the fellahin are infested, it has been estimated that only four per cent show pulmonary involvement. The disease in these has often been developing since childhood and the right ventricle becomes nearly as thick as the left. As this is one of the types of obstructive cor pulmonale an early symptom is fainting on effort. This precedes frank breathlessness, and weakness or a feeling of physical exhaustion is more common than oedema. The characteristic pathological lesion in the lungs is the angiomatid—a microscopic whorl of new vessels in relation to the site of embolism. Radiologically the lesions create tiny nodular diffused shadows rather like those in miliary tuberculosis.

Secondary carcinoma may produce two types of cor pulmonale. Chorion epithelioma

with its propensity for blood vessel invasion can readily embolize the lungs and produce an obstructive cor pulmonale Lymphangitis carcinomatosa (often from stomach or pancreas) usually results from blockage of the thoracic or right lymphatic ducts high in the thorax and diversion of carcinoma cells in a retrograde fashion down the peribronchial lymphatics. The smaller bronchi are then virtually surrounded by a sheath of carcinoma cells which compress them by their growth or by a scirrhous connective tissue reaction thus producing a cyanotic or hypoxic type of cor pulmonale. The picture only rarely creates confusion, but patients may survive the earliest radiological changes by several months.

In sickle-celled anaemia agglutinated masses of abnormal cells may plug the pulmonary vessels with secondary development of obstructive vascular changes.

Pulmonary polyarteritis is said to be the only form of polyarteritis which is associated with an eosinophilia. It is associated with evanescent fluffy shadows in various parts of the lung fields Other systemic manifestations usually dominate the clinical picture and the effects on the right heart are relatively insignificant. Pulmonary embolism acute and recurrent are discussed elsewhere (see Chapter 13)

A commoner diagnostic difficulty is the mixture of features of right and left heart failure in the following ways.

Ischaemic heart disease in a bronchitic.
Bronchitis in a hypertensive subject
Cardiac asthma with gross wheezing
Severe pulmonary oedema with cyanosis and left heart failure.

All these are common disorders in the age group 40 to 70, and on occasions the picture may be mixed and confused Its precise unravelling depends on the fullest clinical study and on various diagnostic aids and pulmonary function tests.

The following features are usually indicative of an aetiology other than pulmonary (Fulton, 1953): (1) cardiac pain, (2) paroxysmal nocturnal dyspnoea, (3) *sudden* increase in dyspnoea, (4) clinical cardiac enlargement, (5) sustained atrial fibrillation, (6) abnormal left axis deviation or left bundle branch block in the electrocardiogram, (7) age over 65 years

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Secondary carcinoma may produce two types of cor pulmonale. Chorion epithelioma

Chapter 12

CHRONIC PULMONARY DISEASE

By PHILIP HUGH-JONES

Chronic pulmonary disease may either cause a maldistribution of blood to different regions of the lungs, or it can alter the total pulmonary vascular resistance and blood flow, leading to pulmonary hypertension and then to right heart failure (cor pulmonale). The latter effect is of much the greater clinical importance.

The exact mechanism of pulmonary hypertension in chronic lung disease is still obscure, but two clinical observations are noteworthy. First, it tends only to occur after the lung disease had been present for a very long time, and lung failure has developed. Lung failure means that the lungs no longer maintain their primary function of keeping the arterial blood gases within the narrow limits of normal, and it is present when the carbon dioxide tension rises or the oxygen tension falls outside these limits in the absence of a right to left cardiac shunt Secondly, cor pulmonale may become obvious, associated with a demonstrable rise of pulmonary artery pressure, during an exacerbation of the chronic lung disease, as with an acute respiratory infection, and then go again on recovery. This episodic change in pulmonary artery pressure contrasts with the persistent pulmonary hypertension of other conditions, such as mitral stenosis Both these observations support the view that reactive vasoconstriction is of great importance in producing pulmonary hypertension in chronic lung disease

The pulmonary artery pressure in some patients with cor pulmonale does not return to normal after recovery from acute infection, and here obliteration of the pulmonary vascular bed may be an important cause of increased vascular resistance But the variations in pulmonary hypertension with changes in arterial blood gas tensions (Whitaker, 1954), and the occurrence of cor pulmonale after many years in patients who only have a chronic inability to ventilate their lungs adequately (such as some cases of kyphoscoliosis who, at post-mortem examination, have no emphysema or other changes in their lungs obliterating the pulmonary vessels), suggests that functional vasoconstriction is most important (see Chapter 4)

As Wood (1956) points out, it is difficult to estimate the absolute frequency of cor pulmonale (Chapter 11) compared with other forms of heart failure, for it is a complication of disease of the lungs, under which it appears in the Registrar-General's reports. But in a recent survey it was found that cor pulmonale accounted for approximately 35 per cent of all cases of congestive cardiac failure admitted to hospital in the Sheffield area (Sheffield Hospitals, 1959) Of the chronic chest diseases emphysema and bronchitis are by far the commonest causes of pulmonary heart failure. The pneumoconioses may be the next commonest cause in some industrial areas, such as South Wales, but elsewhere, kyphoscoliosis and other conditions producing chronic hypoventilation, though themselves

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sense, but use it to mean a functional state which, if diagnosed on definite clinical and ancillary criteria, usually corresponds with true pathological emphysema. Since we shall be talking about a state of altered lung function we shall not be concerned with the different anatomical types of emphysema ("hypertrophic", "centrilobular", "diffuse", etc.) none of which has been shown to have a specific functional significance

In Britain most patients with chronic lung insufficiency, with resulting breathlessness on exertion, who eventually get disturbance of their pulmonary circulation, have a mixed pathology which causes obstruction to the air-flow in and out of their lungs. All or some of the following components are present *chronic bronchitis*, *asthma* (of a chronic non-paroxysmal type) and *emphysema* In this chapter we shall define these components as follows·

Bronchitis: an excessive secretion from the bronchial tree manifest as phlegm.

Asthma: a reversible obstruction to air-flow from the lungs.

Emphysema· a condition defined in terms of morbid anatomy, given above, which gives rise to persistent air-flow obstruction, irreversible by drugs. Its most important clinical feature is undue breathlessness on exertion, not attributable to other specific causes. Clinically, therefore, a diagnosis is mainly reached by exclusion, with positive help from radiology and function tests (Hugh-Jones, 1958b). Positive physical signs are only of value in rather advanced cases (see below)

Since not all patients with the common "chronic chest" complaint have all three components it is best, clinically, to think initially in terms of a general functional diagnosis of "chronic airways obstruction" (just as one may think in terms of "congestive cardiac failure") and then make a careful decision about the role of each causative component. This approach is of great practical importance, and a much better one than loosely calling all such cases "emphysema", because the asthmatic component can be relieved and infection associated with bronchitis can be treated, whereas emphysema itself is a destructive process which cannot be reversed, though some of its effects can be alleviated.

True pathological emphysema usually occurs with antecedent bronchitis (Stuart-Harris and Hanley, 1958; Oswald, 1958) though it may occasionally occur without any bronchitis, a type documented more frequently in the United States Its presence should only be diagnosed with good reason and an attempt made with the help of function tests to determine its severity, for the prognosis in relation to cor pulmonale is much dependent on this

Functional Pathology

Emphysema causes more widespread disturbance of lung function than any other disease. All its effects will be considered in some detail because they provide a basis for discussion of the functional changes in other chronic lung diseases affecting the pulmonary circulation The lungs have two major functions to perform and emphysema disturbs both Their *primary function* is to provide an interface of enormous surface area between the blood and the environment across which *gas exchange* can take place by diffusion; there is a net transfer from blood to air, or vice versa, according to the tension gradient on the two sides of the membrane. Blood is pumped to this interface by the heart, but in land-living animals, such as man, the environmental air has to be pumped to the other side of the alveolar membrane by the lungs themselves which take on a secondary function

relatively uncommon, probably come next. Although cor pulmonale may also occur in the different fibrotic and other chronic lung conditions, it is conspicuous by its absence in many of them. This lack in many chronic lung diseases, such as tuberculosis, except in the most advanced stages (Uggla, 1957), is itself of interest in relation to the aetiology of cor pulmonale. For these diseases may cause extensive local anatomical damage to the lungs and consequent reduction of the vascular bed, but they tend not to cause functional lung failure because there is an adequate reserve of function in the remaining normal lung. Cor pulmonale is particularly associated with those chronic lung diseases which cause changes in overall lung function rather than localized morbid anatomy. Of the functional effects of these disorders chronic hypoventilation is of great importance.

EMPHYSEMA AND BRONCHITIS

Definitions

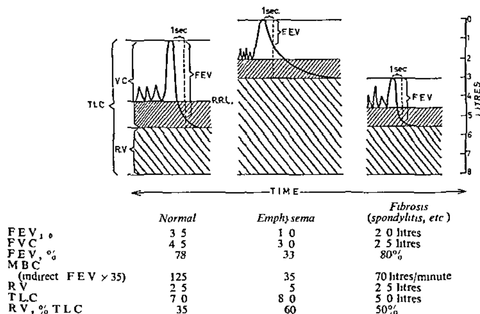
Although this condition disturbs the pulmonary circulation more frequently than any other chronic lung disease, it is not a clearly defined entity.

We are all familiar with the common group of patients who have what is loosely called "bronchitis and emphysema" in this country, but usually just "emphysema" in the United States. Their cardinal symptom is undue breathlessness on exertion In most of them this gradually increases and eventually goes on to lung failure, at first only on exertion, but finally at rest. Most of them, at any rate in Britain, have cough and sputum as well.

The difficulty in definition is the meaning of "emphysema". It is really a term applied to morbid anatomy and in this context there is usually agreement about it. We should strictly use it in the morbid anatomical sense; and a satisfactory definition is: "*A condition of the lung characterized by increase beyond the normal in the size of air-spaces distal to the terminal bronchiole either from dilatation or from destruction of their walls*" (Ciba, 1960). There are two problems about this definition. First, it includes what may have been a temporary over-inflation of the lung in life and there are those who would confine emphysema to those cases where there is actual destruction of respiratory tissue; however, the focal emphysema of coal pneumoconiosis, for example, is a permanent emphysema but limited to dilatation of respiratory bronchioles (Heppleston, 1953). But what to include and exclude within the pathological definition is largely polemic and does not concern us here. Secondly, since lung biopsy is usually impracticable, the clinical diagnosis of emphysema in life depends on various diagnostic criteria (clinical, radiological or physiological), and the results obtained do not necessarily predict the finding of emphysema at post-mortem, though they usually do so in advanced cases. Clinicians often use the term "emphysema" without necessarily applying either strict or agreed diagnostic criteria, so there is much confusion and the diagnosis may be made in life when the pathologist finds little or no anatomical emphysema after death. Conversely, emphysema may be localized at post-mortem, or if generalized, of such a mild degree as to have caused no detectable

muscles by an emphysematous patient attempting to accelerate air-flow may simply narrow the airways and trap gas in the lungs from airways collapse (Campbell, 1958). Such trapping in normal subjects only occurs at the end of the deepest exhalation thereby limiting the expiratory reserve volume and keeping the residual air volume in the lungs, In emphysema the trapping occurs early in expiration and the residual volume is greatly increased. The total lung capacity itself may be raised (Fig 128) but the residual volume always forms an abnormally large percentage of it.

The expiratory airways resistance can become enormous in emphysema during attempts



	Normal	Emphysema	Fibrosis (spondylitis, etc)
F E V 1 0	3 5	1 0	2 0 litres
F V C	4 5	3 0	2 5 litres
F E V, %	78	33	80%
M B C (indirect F E V × 35)	125	35	70 litres/minute
R V	2 5	5	2 5 litres
T L C	7 0	8 0	5 0 litres
R V, % T L C	35	60	50%

Fig 128 Diagram of tracings on a kymograph, as recorded when measuring the F E V 1 0. so that expired volumes are traced downwards The tracings are super-imposed on a representation of the sub-divisions of the total lung capacity The tracings and numerical values given as examples, are only approximate but are typical of the lesions concerned

to increase the minute volume during exercise, and even at rest it is usually increased accounting for the well-known prolonged expiratory phase of breathing. Mead *et al.* (1955) cite an example of a patient who, while applying a pressure difference of more than 80 cm. of water to his lungs, only produced an expiratory air-flow equivalent to that in normal resting expiration.

In gross emphysema the work of breathing may become so great that the oxygen consumption of the respiratory muscles may be a high proportion of the total and there soon comes a point in exercise where any increase in minute volume means an oxygen cost of breathing greater than the extra oxygen intake.

of being an air-pump or bellows for *ventilation*, acting through the agency of chest-wall and diaphragm movement (see Chapter 3).

Defects of ventilation. The maximum breathing capacity (M.B.C.), that is the maximum amount of air that can be breathed per minute, may be grossly reduced depending on the degree of emphysema. Essentially the M.B.C. represents the ventilatory reserve of the air-pump which is available for exercise. Its normal value depends on age, size and sex of the patient. It tends to decrease considerably with age, starting at about 150 litres/min. in young men and dropping to 60–80 litres in the elderly. *In advanced emphysema the* reduction may be gross, reaching as low as 15 litres/min., so that there is virtually no ventilatory reserve for the slightest exercise.

The reduction of M.B.C. in emphysema is far more significant than the reduction in vital capacity (V.C.). The latter is usually reduced, but not necessarily as severely as in diseases causing restriction of chest movement (lung fibrosis, ankylosing spondylitis, etc.). The M.B.C. is disproportionately low in emphysema because of obstruction to air-flow. An emphysematous patient taking a long time to "blow out" a vital capacity test may achieve a good score, but he cannot get the air out quickly (as he has to do when he is panting during exercise) Thus, the efficiency of the lung as an air exchanging bellows for maximum exercise is better measured by the volume of air exhaled in *a given time* from the start of quick maximum expiration following a full inspiration, rather than by the vital capacity. This volume exhaled in a given time in these circumstances is called the "forced expiratory volume" (Gandevia and Hugh-Jones, 1957) and the time interval usually adopted for its measurement is one second. The F.E.V. can be measured easily by getting a patient to exhale his vital capacity *quickly* and forcibly into a suitable spirometer and recording the movement of the bell on a kymograph. The full amount exhaled is the forced vital capacity (F.V.C.). *In normal subjects and most patients this is about the same as the* vital capacity performed slowly, but in emphysema it may be less (because of air-trapping in the lungs) (see below) For our purpose the V.C. and the F.V.C. can be treated as synonymous

The forced expiratory volume measured for a second (F.E V $_{1\cdot0}$), is about 75 per cent of the vital capacity in normal subjects. With air-flow obstruction, as in emphysema or asthma, the expiratory *flow curve is slowed and the one-second F.E.V. is disproportionately* reduced compared with the V C. It may only measure about 40 per cent of the latter With a purely restrictive lesion, such as ankylosing spondylitis, the vital capacity is reduced but the F.E.V. forms over 80 per cent of it (Fig. 128).

When a patient is panting maximally, one breath is like another and the relation of inspiratory to expiratory flow pattern sufficiently constant to permit prediction of the M.B.C. from the F.E.V. by multiplying the latter by a rate factor (approximately 35 for the F.E.V.$_{1\cdot0}$). Multiplication of the F.E.V. by a constant is, of course, unnecessary and the F.E.V. itself can be used as a measure of the patient's M.B.C.

The obstruction to air-flow in emphysema differs from that in asthma, although asthma secondary to bronchitis may be present as well and form part of the obstruction. In uncomplicated emphysema, the obstruction is caused by expiratory collapse of the airways consequent upon loss of elastic recoil in the lungs. Expiration is normally passive from elastic recoil which drives the air up the airways, when it maintains the pressure above that of the intrapleural space. Any increase in intrapleural pressure, from the use of expiratory

1952), and thus the onset of cor pulmonale seems to be most closely related to the progressive reduction in vascular bed that occurs" Unfortunately, the interpretation of the carbon monoxide test is very complex. In one form it may be markedly influenced by ventilatory inequality in the lungs (Marshall, 1958) so that its reduction does not necessarily mean a reduced vascular bed When performed by the single-breath technique, however, the effect of ventilatory inequality is less. Then a reduction in the test value is found only in advanced cases of emphysema and mainly those in whom the condition developed rapidly with little antecedent-bronchitis (Ogilvie, 1959)

Functional variations. This review of the functional pathology of the average patient with emphysema has indicated that every aspect of lung function may be disturbed But the emphysematous process may vary from a negligible to a gross degree in different patients Even if it is fairly advanced, not all aspects of lung function are necessarily disturbed to the same extent. Thus some patients appear to have more ventilatory disturbance and become dyspnoeic without cyanosis. Others have gross disturbance of gas exchange with cyanosis out of proportion to their dyspnoea Many advanced cases have both ventilation and gas exchange seriously disturbed

To understand the clinical features of emphysema in relation to pulmonary hypertension and cor pulmonale, it is important to appreciate some effects of disturbance of ventilation and gas exchange on the arterial blood. The effects of overall hypoventilation alone must be distinguished from the effects of lack of balance between ventilation and perfusion.

Hypoventilation Excessive work of breathing in emphysema may reflexly limit ventilation though over-stimulation of stretch receptors in the lungs and hypoventilation results It has been shown by animal experiments (Davis *et al.*, 1956) that stimuli in these receptors are related to the work of breathing, and in man these stimuli to the respiratory centre may in some circumstances be of greater importance even than carbon dioxide (Fowler, 1954).

Normally, the alveoli are ventilated with fresh air in sufficient quantity to dilute the carbon dioxide produced by metabolism so that its partial pressure in the alveoli, and hence in the arterial blood (for carbon dioxide diffuses so readily that there is usually negligible tension gradient for this gas between the two) is very close to 40 mm Hg There is a fundamental relation·

$$P_{ACO_2} = \frac{0{\cdot}863 \times \dot{V}_{O_2} \times R}{V_A}$$

which shows that alveolar carbon dioxide tension (P_{ACO_2}) varies directly as the oxygen consumption but inversely with the alveolar ventilation Here, 0·863 is a factor depending on temperature, pressure, etc., and the product $V_{O_2} \times R$ (oxygen consumption × respiratory quotient) is the carbon dioxide produced per minute which, for a given quotient depends on the patient's activity, as reflected by the oxygen consumption. Thus, if alveolar ventilation is increased, without a change in metabolism as in voluntary over-breathing, the arterial and alveolar P_{CO_2} fall. This is *hyperventilation*. Conversely, the carbon dioxide tension falls in alveolar ventilation is reduced without a decrease in metabolism, and *hypoventilation* results. The respiratory centre normally adjusts the ventilation correctly in relation to the arterial carbon dioxide tension.

All these defects in the lungs as bellows contribute towards hypoventilation which we shall see is a factor of importance in producing pulmonary hypertension and cor pulmonale.

Defects of Gas exchange. Gas exchange can be affected in two ways by emphysema: first, because of uneven distribution of gas and of blood over the interface in the lungs, and secondly through reduction in the total surface area of this interface.

Uneven ventilation and perfusion Emphysema tends to be distributed in patches through the lungs so that the time-constants for filling or emptying of different areas vary (Otis *et al.*, 1956), some areas filling more completely during breathing than others. Thus there is unequal ventilation. This can be detected by various procedures in which an analysis of expired gas is made, and these are helpful diagnostically (Fowler, 1949; Bates and Christie, 1950, Comroe and Fowler, 1951; Briscoe *et al.*, 1951; Gilson and Hugh-Jones, 1955).

Uneven ventilation obviously means that not all parts of the large lung interface are effectively used for gaseous diffusion, but its real significance must be considered in relation to blood distribution. If the poorly ventilated parts are also poorly perfused by blood, they are functionless for gas exchange, and the lung has simply lost some of its enormous surface area But if well-ventilated areas are not perfused they act as dead space and waste part of each tidal volume of air; conversely if badly ventilated areas are well perfused they act as a virtual shunt of blood and some "venous-admixture" takes place into the arterialized blood leaving the lung. Thus, in the absence of any barrier to diffusion across the interface, the gas composition of the arterial blood is solely determined by the integrated total of the gas composition of blood leaving each alveolar capillary, and this is entirely dependent on the ventilation-perfusion ratio within the alveolus. Thus the arterial blood gas composition is affected by the ventilation and pefusion being "out of step" but it is unaffected if uneven distribution of air is compensated by a similar disturbance of distribution of blood flow.

As a general rule in lung disease poorly ventilated alveoli are also poorly perfused. Emphysema is almost the sole condition in which serious "out of balance" or inequality of ventilation-perfusion ratios occurs. However, recent work (Riley *et al*, 1951; West *et al.*, 1957; Read and Williams, 1959) has shown that some emphysematous patients have their uneven ventilation balanced by a corresponding unevenness of perfusion more than others Thus, even if ventilatory inequality is severe it may be "compensated" by perfusion change and different degrees of compensation may be recognizable.

Reduced diffusing capacity. The diffusing capacity of the lungs is usually measured by testing the subject's ability to remove carbon monoxide from an inspired gas mixture of air with a little (about 0·2 per cent) carbon monoxide added (Chapter 3), either during a period of breath-holding after a single inspiration, or during a multiple breath steady-state procedure. Carbon monoxide is used as the test gas, rather than oxygen, because its uptake is practically only limited by the diffusing capacity of the lung interface and not by blood flow and other factors. Emphysematous patients often show an abnormal reduction in their ability to take up carbon monoxide for a given tension of that gas in their alveoli. Bates (1958) has suggested that low carbon monoxide test values in emphysema reflect the reduced surface area of alveoli and that "the progressive loss of vascular bed probably results in the pulmonary hypertension found in emphysema (Mounsey *et al.*,

perfusion ratios in the lung causes hypoxia, without hypercapnia. However, in emphysema, the required increase in ventilation often cannot occur, because of the mechanical problems In that case, there is carbon dioxide retention as well as gross hypoxia because of overall hypoventilation as well as ventilation-perfusion imbalance.

In summary, pure overall hypoventilation (from whatever cause) gives rise to hypercapnia and to hypoxia proportionally If a ventilation-perfusion imbalance exists too,

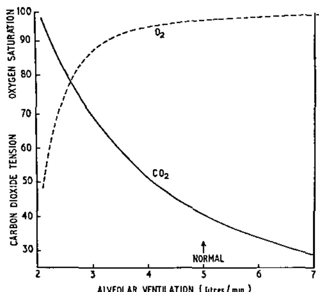


FIG 129 Relation between alveolar ventilation and the arterial oxygen saturation and carbon dioxide content

then the hypoxia is out of proportion to the hypercapnia and central cyanosis (which means severe hypoxia) often appears. A ventilation-perfusion imbalance is the commonest cause of central cyanosis of pulmonary origin.

Clinical Features

Symptoms and signs. The characteristic symptom of emphysema, itself, is progressive exertional dyspnoea Cough and sputum which are usually, but not always, present are the symptoms of bronchitis Wheezing is usually the symptom of any non-spasmodic asthma which may accompany the emphysema and bronchitis. If heart failure occurs the dyspnoea becomes more intense and the patient may complain of oedema.

The chest is held in the inspiratory position with consequent limitation of expansion and a tendency for "*movement en bloc*" or lifting of the sternum with early use of scalene and sternomastoid muscles Many emphysematous patients are thin and have bright rather protruberant eyes There is often in-drawing of the intercostal spaces on inspiration but a barrel-shaped chest is by no means a necessary feature, even of advanced

Note, in this discussion it is the alveolar ventilation and not the total air going in and out of the nose and mouth, or *minute volume*, which is the critical factor. Alveolar ventilation is:

(tidal volume − dead space) × frequency of breathing.

In emphysema the dead space may be increased above that of the upper airways or anatomical dead space, because of ventilation of unperfused alveoli and an abnormally large proportion of inspired gas takes no part in alveolar gas exchange. Thus when a patient with severe emphysema has an overall ventilation (minute volume) at rest which is the same as or even greater than that of a normal subject he may be hypoventilating Only the alveolar or the arterial carbon dioxide tension truly reflects the adequancy of the ventilation.

Some emphysematous subjects do maintain an adequate alveolar ventilation in spite of an increase in dead space, a large minute volume and an excessive work of breathing. They complain of dyspnoea, probably from the excessive stimulation of their lung stretch receptors. Others, as it were, give up the struggle of dyspnoea, the excessive stimuli from the pulmonary stretch receptors overcomes the effects of carbon dioxide, and they "accept" hypoventilation and a raised alveolar and arterial carbon dioxide tension even at rest. Their respiratory centre becomes adjusted to the hypercapnia and insensitive to carbon dioxide (Prime and Westlake, 1954, Donald and Christie, 1949). Such patients have been called "lazy-breathers" by Dornhorst (1955) On command they can voluntarily increase their ventilation and lower their carbon dioxide tension to normal and if their mechanical defect can be improved (for example by removing any added asthma and accompanying bronchitis) the response of their respiratory centre to carbon dioxide improves (Cherniack and Snidal, 1956).

The effect of hypoventilation is to raise the arterial carbon dioxide tension and lower the oxygen tension proportionately. But because of the shape of the oxygen dissociation curve hypoventilation does not readily give rise to cyanosis (Fig. 129). Thus with a normal respiratory quotient and alveolar ventilation of about 5 litres/min. the P_{CO_2} is 40 mm. Hg and the oxygen saturation 97 per cent. If the alveolar ventilation falls as low as three litres/min. the P_{CO_2} rises to almost 80 mm. Hg but the saturation is still about 85 per cent, at which level cyanosis is barely detectable. But, again because of the shape of the oxygen dissociation curve, this degree of unsaturation represents a profound fall in oxygen tension from the normal of about 100 mm Hg to about 60 mm Hg. Thus, hypoventilation causes hypercapnia and a corresponding degree of hypoxia, but no cyanosis except when it is extreme.

Ventilation-perfusion imbalance. In contrast to hypoventilation, inequality of distribution of gas and blood within the lungs tends to cause hypoxia without hypercapnia. In those parts of the lung in which perfusion is excessive compared with their ventilation, the blood leaves with a reduced oxygen tension but a raised carbon dioxide. The latter stimulates the respiratory centre and causes an increase of overall ventilation. Such an increase in parts originally normally or excessively ventilated compared with their perfusion will eliminate carbon dioxide but can only add a negligible amount of oxygen since their blood is already being almost fully oxygenated when it passes to the pulmonary vein. Thus, if a compensatory overall hyperventilation can take place, inequality of ventilation-

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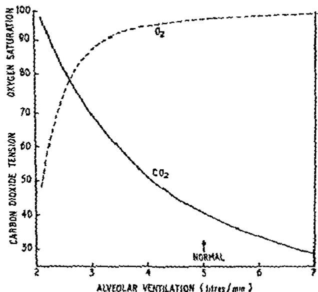


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emphysema. A diminished cardiac dullness on percussion with downward displacement of the upper limit of liver dullness, and heart sounds almost inaudible, except in the epigastrium, is found in advanced cases. The breath sounds are likewise diminished, sometimes they are entirely obscured by expiratory wheeze and rhonci from accompanying bronchitis The signs of cor pulmonale are dealt with in Chapter 11. Clubbing is not a feature of uncomplicated emphysema; its presence suggests other features such as bronchiectasis or the development of lung cancer, the appearance of the latter often being especially difficult to detect in patients with emphysema and bronchitis.

Radiology. One of the most striking things about the radiograph in emphysema is often how slight the changes are when the patient is seriously disabled. The radiograph, in fact, reflects anatomical rather than functional change. Nevertheless, radiology can be very helpful in aiding the true diagnosis of emphysema in the group of "chronic bronchitis and emphysema" patients. Exaggerated inspiratory posture with flattened diaphragms can be seen, but most important, a disparity between few and thin vascular markings at the periphery of the lung fields compared with the often exaggerated vascular markings at the hilum (Barden, 1952). The latter is especially noticeable when cor pulmonale develops. Tomograms are especially useful for showing the deficiency of the peripheral vasculature when emphysema is present, in contrast to the well-preserved peripheral vessels in patients with uncomplicated spasmodic asthma (Fraser and Bates, 1959).

Local bullae do not themselves mean there is generalized emphysema, though their presence lends support to the diagnosis made on other criteria. Inspiratory and expiratory films may be useful to demonstrate poor diaphragmatic movement which again supports the diagnosis. Radiotranslucency in the lung fields can be helpful, if localized, but the diagnosis of generalized emphysema from apparent overall hypertranslucency may be most *misleading as the appearance depends so much an radiographic technique* (Chapter 5).

Course and complications. In the uncommon varieties of emphysema chiefly seen in younger subjects the course may be rapidly progressive; but in the common cases which are generally accompanied by bronchitis and gradually manifest themselves in middle age, the disease may go on for years with only gradually increasing symptoms and finally end in cor pulmonale. But at any stage an acute upper respiratory tract infection may prove far more serious than in normal subjects, may precipitate cor pulmonale or may even prove fatal.

Acute exacerbations. A cold, influenza or bronchitis, readily gives rise to an extensive bronchiolitis or patchy bronchopneumonia in these patients. *S. pneumoniae*, *H. influenzae*, *E. coli* or *B. pyocyaneus* are the common infecting organisms.

A normal person catching pneumonia and getting some parts of the lung thereby under-ventilated responds by a general increase in ventilation in response to the high carbon dioxide content of blood leaving the under-ventilated areas. As discussed in the section on ventilation-perfusion imbalance, above, *the consequent over-ventilation of the remaining* [illegible]

[illegible] cyanosis, he has a high minute volume, but no hypercapnia. In contrast, the patient with emphysema and bronchitis is usually hypoventilating even before the acute respiratory

infection, because of the gross mechanical disturbance of his chest and the excessive stimuli from pulmonary stretch receptors With the acute exacerbation he cannot respond to the increased ventilation-perfusion imbalance by increasing his minute volume without undue distress, so he becomes more hypercapnic and even further hypoxic than he was with his original hypoventilation. The clinical picture is usually one of ventilatory distress, with the accessory muscles of breathing being used, cyanosis, twitching of the outstretched hands, peripheral vasodilation, engorged veins in the eye fundi and sometimes papilloedema, and a raised venous pressure in the neck.

Oxygen given to these patients with an acute exacerbation readily removes their cyanosis caused by the ventilation-perfusion imbalance. But since their respiratory centre is insensitive to carbon dioxide and breathing is related to the stimulus of hypoxia their ventilation may fall further when the hypoxia is removed by oxygen administration Thus there is a further rise of arterial carbon dioxide tension The latter may be so severe as to cause drowsiness or even coma (Westlake *et al*, 1955) Even without an acute infection, hypoventilation may cause enough cerebral vasodilation from carbon dioxide retention to give headache; with an acute exacerbation papilloedema and a raised C S F pressure may be so marked that intracranial space-occupying lesions are suspected by those who are not on the look out for hypoventilation

With an acute exacerbation, cor pulmonale, which was possibly sub-clinical in the uncomplicated state, often becomes manifest It probably arises from the reactive pulmonary hypertension, together with the high cardiac output, polycythaemia and increased blood volume which these severely hypoxic patients get. That it is the hypoxia rather than the increased carbon dioxide tension which causes the pulmonary hypertension (Chapter 4) is suggested by the right heart strain seen in some residents at high altitude who get hypoxia but not hypercapnia With successful treatment returning the arterial blood gas tensions to normal, the pulmonary hypertension decreases to its original level before the exacerbation. The latter probably depended, at least in part, on the extent to which the pulmonary vascular bed had been reduced by the emphysema and on the degree of hypoxia from continuous hypoventilation.

Polycythaemia Secondary polycythaemia is rather an uncommon complication. Its incidence is puzzling Although it only occurs in those who are persistently rather severely hypoxic (and hence usually cyanosed) there are, on the other hand, many emphysematous patients who are persistently cyanosed and yet not polycythaemic. It has been suggested that the common bronchitic infection in these patients suppresses the reaction of the bone marrow or that iron utilization is impaired. However, recent work (Shaw, 1959) using radioactive labelling of blood iron, shows that the bone marrow responds normally to the stimulus of hypoxia in emphysema by producing more erythrocytes During increased hypoxia from an acute exacerbation red cell production exceeds destruction and the total red cell volume, in general, reflects the degree of chronic hypoxia The reason why some patients with an increased total red cell volume have a high haematocrit and not others is that some also have an increased plasma volume Thus, "polycythaemia" is missed if the diagnosis is based on the haematocrit or haemoglobin per 100 ml rather than on the total red cell volume Presumably those apparently hypoxic patients who are in incipent cor pulmonale have an increased plasma volume which masks polycythaemia. But although there is no conclusive evidence on this point, it is possible that some patients

may respond to hypoxia normally, with increased red cell production, but also respond with increased cell destruction and so not get polycythaemia.

The importance of polycythaemia in disturbances of the pulmonary circulation is that the increased blood viscosity and blood volume may contribute slightly to the circulatory impairment.

Diagnosis

Although the clinical picture may be very variable, depending as we have seen on the extent of the different functional abnormalities, the diagnosis in advanced cases can usually be made on clinical grounds with the help of the radiograph. Since breathlessness without other obvious cause is one important feature the diagnosis is rather one of exclusion, and lung function tests are of positive diagnostic help. But there is the difficulty of suspecting emphysema wrongly in patients who simply have chronic bronchitis and non-paroxysmal asthma. This can be especially difficult when such patients have an acute exacerbation. There are a fair proportion of patients who on clinical grounds in life are thought to have even advanced emphysema with respiratory failure, yet none is found post-mortem, the airways obstruction and hypoventilation being caused entirely by bronchitis or bronchiolitis.

Some truly emphysematous patients with predominant hyperpnoea are thought to be hysterical. Here again lung function tests help in establishing the true diagnosis Left ventricular failure may often be confused with emphysema when it presents predominantly with mechanical disturbance in the chest. True polycythaemia can be confused with emphysemata in patients who have a predominant ventilation-perfusion imbalance and secondary polycythaemia. Morning headaches may take the patient to a neurologist and if gross carbon dioxide retention is present causing papilloedema a false diagnosis of cerebral tumour or other intracranial lesion can easily be made We have seen such cases, and they have been reported elsewhere (Conn *et al.*, 1957).

Patients with uncomplicated paroxysmal asthma very seldom get emphysema and a history of this complaint is against the diagnosis. However, chronic non-paroxysmal asthma with bronchitis can be most difficult to differentiate from emphysema. In fact it is usually not a problem of differentiating it from emphysema but of saying in a patient with chronic non-specific lung disease how much bronchitis, how much asthma and how much emphysema there is. Of the simple lung function tests, a rise in the F.E.V. as a percentage of the V.C. after energetic bronchodilator therapy is against the diagnosis of emphysema, in which condition the F.E.V. per cent remains low (30–50 per cent) even after a full course of such treatment (Thomson and Hugh-Jones, 1958). Arterial blood gas analysis demonstrating carbon dioxide retention is likewise a valuable and simple test But neither of these two is specific and in some difficult cases clinical features, radiographs and full function tests may all be needed to establish the diagnosis

Treatment

General. Any asthma present can be treated with bronchodilator drugs, any infected bronchitis can be treated by antibiotics and postural drainage, but there is little treatment for emphysema itself, though some of its effects can be ameliorated. Thus assessment of each element present is an essential requisite to successful treatment.

Asthmatic element. The most useful oral bronchodilator drugs are Tabs. ephedrine

hyd. (B P.) 30 mg b i.d. or nightly, choline theophyllinate 200 mg. q.d.s. or isoprenaline sulphate 10 mg., sublingually, as required. Exact dosage and frequency are obviously an individual problem for each patient. Ephedrine and isoprenaline may both cause palpitations, and urinary retention in elderly men with enlarged prostates. Any of these drugs, especially choline theophyllinate, may well be combined with the use of either adrenaline and atropine compound spray (B P.C.) or isoprenaline sulphate spray (B P.C) from a suitable hand nebulizer as required. Measurements of the forced expiratory volume before and after the use of such inhalations are most desirable to see what, if any, effect they are producing before given them to the patient Moreover, it is essential that a suitable design of nebulizer be used, which produces a fine mist; and that the patient gets personal instruction in its use, learning first to be sure that a spray is being produced and that the jet is not blocked, and then how to use the inhaler during two or three deep breaths through the mouth If real care is taken then a nebulizer can be most effective in removing labile airways obstruction. The argument that patients "get addicted to these pumps" seems unwarranted if by their use real relief is obtained; over-indulgence in any form of effective therapy may occur unless patient and physician co-operate to prevent it! These hand-nebulizers or automatic pressure aerosols ("Medihaler") of isoprenaline or of adrenaline are one of the most useful methods of relieving labile airways obstruction

If patients fail to respond well to the above bronchodilator drugs, steroid therapy with cortisone, prednisone, prednisolone or corticotrophin may be considered. But the use of these drugs is really fraught with danger of addiction and of serious side-effects It is probably less easy to over-dose cortisone than the others. But whichever is used any form of maintenance dose should be as low as possible compatible with improvement and relief, rather than necessarily trying to remove all labile air-flow obstruction There are many patients in whom a small daily dose of steroids (10 mg. of cortisone or its equivalent) seems to potentiate the use of a hand-spray. In any case it is most important to measure the effect of the steroid on the F.E V. to avoid confusion with its psychological effects

Finally, long-acting ephedrine, in the form of ephedrine resinate, or suppositories of aminophylline may do much to improve ventilation and prevent early morning headaches of which many patients with advanced emphysema and bronchitis complain

Whatever bronchodilator therapy is used regular measurement of the forced expiratory volume or other similar index of air-flow is the only really satisfactory way of assessing progress.

Bronchitis element. There is the very obvious preventive need to avoid bronchial irritation as much as possible. In this country it is difficult for patients living in towns to avoid fog, but smog masks and small concentrations of ammonia in the air of the home during fogs (*British Medical Journal*, 1955) help to alleviate the effects Even more obvious is the avoidance of cigarette smoking, yet most patients with emphysema and bronchitis are either unwilling or unable to stop!

If the bronchitis is infected and the sputum purulent antibiotic treatment should be [illegible]

immediately should diarrhoea occur), are one of the most useful drugs for chronic bronchitis (Elmes *et al* , 1957) Chloramphenicol is often even more effective, especially when

H influenzae is the main pathogen in the sputum (Douglas *et al.*, 1957). Its toxic effects in the bone marrow have probably been over-emphasized. Nevertheless, because of this remote danger, most physicians reserve its use in bronchitis for middle-aged or elderly patients and then avoid prolonged or repeated courses of it. Other antibiotics especially penicillin (often given orally as "V" or phenoxymethyl-penicillin), streptomycin, erythromycin all have their place but a discussion of their use, limitations and dangers is outside our scope here.

Emphysematous element. There is no specific treatment. Once the asthmatic element, when present, is removed the remaining expiratory air-flow obstruction from loss of elasticity can only be helped by such measures as breathing exercises (the value of which is doubtful from evidence obtained by testing lung function, but they may have a justified psychological value and help in maintaining slow expiration) or possibly by intermittent positive pressure breathing (I.P.P.B.) in the out-patient department. It is difficult to see why I.P.P.B should be of any permanent value itself, and some of the enthusiastic reports of its benefit from the United States (Motley *et al.*, 1948, Sieker and Hickam, 1956; Sieker *et al.*, 1956; Hickam *et al*, 1957) may simply reflect the undoubted benefit from bronchodilator drugs whenever there is accompanying asthma, for the reports describe its use in conjunction with bronchodilator aerosols (Fowler and Miller, 1958). It is, however, clearly of value in extreme carbon dioxide narcosis (see below).

In advanced cases of pulmonary hypertension the heart is involved (cor pulmonale) (Chapter 11). The place of venesection in such cases is debatable, but it may help (Auchinloss and Duggan, 1957). But both for preventive and curative treatment of pulmonary hypertension ambulant oxygen therapy should be carefully considered in a few selected cases with advanced disease. Portable oxygen (Cotes and Gilson, 1956b) is difficult to administer in normal social circumstances and the likely benefit to the patient needs

1956a; Campbell, 1957)

In patients who show chronic hypoventilation attempts have been made to increase the minute volume by drugs, such as aspirin, which stimulate the respiratory centre. But although headache and mental clouding may be improved, and it is possible that pulmonary hypertension can be reduced by this means, the resulting sensation of breathlessness has made the treatment intolerable in all patients we have studied. It may be that in future, such treatment would be feasible if it could be combined with surgical division of nerves from pulmonary stretch receptors, but this is not yet really practicable.

In advanced cases with a grossly diminished effort tolerance, extreme work of breathing, and much sputum a permanent tracheostomy is of real benefit. The reduction of upper respiratory dead space diminishes the minute volume for a given alveolar ventilation and the patient can learn to suck out secretions through the tracheostomy with a

removes some of the problems associated with a permanent [illegible]
et al., 1958).

It has been claimed that a pneumoperitoneum may help a patient to use his flattened

diaphragm and so ease his breathing, but we have not found this to be so in one or two cases in which this treatment has been done. But surgical removal of large emphysematous bullae, together with stripping the nerve plexus at the roots of the lungs, can be of help in the few patients where it is indicated. The indication is not really the removal of unventilated or underperfused lung, which was giving rise to increased dead space or venous admixture, but it is when the tension within the cyst or cysts is such as to augment the air-trapping in the rest of the lung. In solitary cysts in normal lungs the cyst tension must get large before a significant adverse effect on expiratory airways resistance occurs; but if the cyst or cysts are in emphysematous lung, where airways resistance is already excessive from trapping, a small rise of tension and enlargement of the cyst may become of critical importance Again, assessment of such patients before operation at a suitably equipped centre is desirable, and removal of cysts or bullae in patients with minor symptoms is not justified.

Acute exacerbations Accurate diagnosis is essential before treatment is begun In a seriously ill patient it may be very difficult to differentiate between left-sided heart failure with pulmonary oedema and an acute exacerbation of emphysema or bronchitis with respiratory failure The clinical differential diagnosis is discussed by Westlake (1955) Opiates which are indicated in left-sided failure are highly dangerous and often fatal, even in very small doses, in patients with any degree of respiratory failure.

The precipitating infection is immediately treated with antibiotics, best in combination, before waiting for the results of bacterial examination of the sputum But it is important to send sputum for examination whenever practicable so that the antibiotic treatment can be adjusted later, if necessary. Treatment of heart failure is instituted (Chapter 11) and oxygen is given. The oxygen must be wetted and if, as is usually the case, there is asthmatic wheezing, a suitable nebulizer (such as that designed by Wright, 1958) with water, adrenaline, or isoprenaline 4-hourly can be used as the mode of wetting the oxygen Steroids should be considered in rare cases where there is evidence of adrenal insufficiency This may well arise in any bronchitic or asthmatic patient who has had therapeutic steroids and then gets an acute chest infection

On such a regime, using continuous oxygen, the ventilation may fall and carbon dioxide retention become extreme even causing drowsiness or coma. Fear of this is not an indication to withhold oxygen, for the hypoxia is of such importance in maintaining pulmonary hypertension. But its occurrence is an indication for augmenting ventilation and so returning the arterial carbon dioxide to a satisfactory level This can usually be done by analeptic drugs The best are either nikethamide or amiphenazaole by injection. Intravenous aminophylline or amphetamine are other useful, but rather less effective, alternatives The dose depends on the patient's response, and large and repeated doses may be needed. The B P. dose of 2 ml of nikethamide should be given initially and if that is not enough, 5 or even 10 ml may be needed The effect of the right dose is usually dramatic in causing the patient to wake up and to ventilate and cough adequately. The dose may need repeating at up to half-hourly intervals and an infusion of the drug in an intravenous drip may be indicated. There is a suggestion that therapeutic stimulation of ventilation without the advent of fits, which will occur from overdosage of such drugs, is more easily achieved with amiphenazole than with nikethamide, though we have found the latter quite satisfactory in large numbers of patients

In a few cases of acute respiratory failure tracheostomy should be done. The decision for tracheostomy is not an easy one since, with the above regime, many patients recover without it. But if there is an excess of secretions or the patient is coughing inadequately tracheostomy should be done, especially if the response to nikethamide is poor. Once done artificial mechanical ventilation through the tracheostomy can be lifesaving, details of the management of these patients is beyond our scope here (Hugh-Jones, 1958a; 1959). In elderly patients with gross emphysema, tracheostomy and mechanical ventilation are not indicated, any more than the use of the artificial kidney is indicated when there is little prospect of recovery in renal failure. The difficulty is in younger patients, where during the acute emergency, the amount of emphysematous destruction of the lung cannot be gauged. Such patients should be given the benefit of tracheostomy and artificial ventilation if needed, though with the use of oxygen and analeptics in adequate dosage the number requiring artificial ventilation are few.

It is interesting and rewarding to note how in most cases right-sided heart failure responds to prompt action in restoring the arterial blood gases back to normal by oxygenation and ventilation. This finding fits the observations of Mounsey *et al.* (1952) and Whitaker (1954) on the variations of pulmonary artery pressure in patients with cor pulmonale and emphysema.

PNEUMOCONIOSIS

It is convenient to divide the dust diseases into those caused by vegetable and those caused by inorganic mineral dusts. Of the former only farmer's lung and the byssinosis of the cotton industry, which produces an unusual type of asthma, sometimes cause permanent lung damage which may terminate with cor pulmonale (Schilling, 1956). Of the mineral [illegible] virtually no functional [illegible] pulmonary hypertension and right-sided heart failure in their late stages Asbestos and beryllium both produce the functional lesion of "alveolar-capillary block" associated with interstitial fibrosis, which is entirely different from the changes caused by coal pneumoconiosis or silicosis. They rarely cause pulmonary hypertension and are mentioned with other examples of interstitial fibrosis later.

Coal Worker's Pneumoconiosis

Pathology. There are two distinct processes. The first "simple pneumoconiosis", is caused by retention of coal dust of fine particle size over many years, and it gets worse only if dust exposure continues. The second "complicated pneumoconiosis" results from an infective process ("progressive massive fibrosis" or P.M.F.) almost certainly due to the tubercle germ, which is superimposed on the simple pneumoconiosis. It only occurs in the presence of advanced simple pneumoconiosis, and behaves quite differently from ordinary tuberculosis; it can be acquired and get worse, independently of any further dust exposure (Fletcher, 1948; Cochrane and Carpenter, 1956).

[illegible] "coal nodules" [illegible] part of the lung, [illegible]

though the respiratory bronchioles may become distended and produce "focal emphysema" (Heppleston, 1953). As the coal foci get more abundant they gradually produce the characteristic radiological appearances of simple pneumoconiosis. In the International Classification (1950) of the radiographic appearances of pneumoconiosis three stages of simple pneumoconiosis are recognized, called simply categories one, two and three according to the density of the characteristic minute opacities. P M F is only found superimposed on at least radiological category two simple pneumoconiosis. At first it is often difficult to distinguish it radiologically from true tuberculosis. Soon, however, the shadows of it enlarge to give the characteristic "massive shadows" which represent a solid mass of coal-impregnated fibrous tissue. They may cavitate from avascular necrosis causing profuse "black spit", and finally the whole chest architecture is disturbed



(*a*)



(*b*)

FIG 130a and b Examples of the radiographic appearances in coal-workers' pneumoconiosis (*a*) Simple pneumoconiosis, category 3, (*b*) Complicated pneumoconiosis with P M F, category C

by these spreading masses causing kinking of the trachea and bullae at the lung bases. Four radiological stages of massive fibrosis are recognized, stages A, B, C, and D. Typical examples of the radiographic appearances of coal pneumoconiosis are shown in Figs. 130a and 130b.

There is none of the characteristic constitutional upset which is associated with active tuberculosis in patients with P M.F, except in a very small proportion of men (about three per cent), in which the sputum becomes positive and who then resemble patients with overt tuberculosis.

Clinical course and functional change. The main effect of coal-workers' pneumoconiosis is to cause excessive breathlessness on exertion. This is mainly related to a reduction in the maximum ventilatory capacity of the lungs, though in advanced cases there is also an increased ventilatory requirement for exercise. Simple pneumoconiosis hardly causes any increase in breathlessness over that which develops in normal men with increasing

age, in complicated pneumoconiosis, on the other hand, *breathlessness is often severe* Many patients with simple pneumoconiosis never get the complicated disease and pulmonary hypertension, and right heart failure are not seen as the result of simple pneumoconiosis. But it is a frequent accompaniment of the late stages of complicated pneumoconiosis. About half of the men with category D complicated pneumoconiosis show right heart stress Thus, once massive fibrosis is acquired, pulmonary hypertension usually follows after a number of years. Nevertheless, severe cor pulmonale is much less common (even in advanced pneumoconiosis) than it is in non-industrial emphysema and bronchitis. This may well be related to the relative lack of hypoxia in pneumoconiosis except in the advanced disease (Gilson and Hugh-Jones, 1955).

Silicosis

Silica dust, unlike coal, produces a marked fibrous reaction by the lung. Thus the nodules of simple silicosis consist of hard pea-like masses of whorled fibrous tissue in the lungs, and the radiological appearances tend to become those of discrete pea-like nodules scattered throughout the lung fields. *In typical cases they are sharp in outline* and the appearance is quite different from the minute ("pin-head") opacities of coal pneumoconiosis. In some cases the hilar glands become calcified to give an "egg-shell" appearance.

Massive shadows occur with tuberculous infection and overt silico-tuberculosis is much more common than in coal dust disease. In the early experience in the South Africa diamond mines most of the sufferers from silicosis died from tuberculosis. McCann (1937, 1939) stressed the interrelation of cardiovascular and pulmonary failure in silicosis but mentions that miners with coal pneumoconiosis live longer than men with silocosis and hence seem more frequently to get cor pulmonale. Pulmonary hypertension and cor pulmonale develops with massive silicosis after a long period of time, as it does in coal pneumoconiosis

ABNORMALITIES OF THE CHEST WALL

There is a group of chronic chest diseases in which there is mechanical limitation of movement of the chest wall causing chronic hypoventilation. The lungs themselves may be entirely normal or secondarily affected; *yet even if they are normal, reactive pulmonary* hypertension may occur, presumably because of the chronic hypoxia, and then cor pulmonale.

Kyphoscoliosis

Many patients *with gross thoracic deformity maintain a limited but quite good* exercise tolerance for years and then, rather suddenly and usually about 20–40 years old, they develop signs of congestive cardiac failure and often die within about six months of its onset.

It is often held that such patients develop emphysema of their lungs and that the functional pathology associated with this is the cause of the circulatory failure. But this explanation is rarely true, and observations on 15 kyphoscoliotic patients by Fishman *et al* (1956) (during which tests of lung function were done as well as heart catheteriz-

ation, together with bronchiography and angiocardiography for estimating distortion of the thoracic structures) showed that generalized alveolar hypoventilation is the prime defect which leads to arterial hypercapnia with a corresponding degree of hypoxia. This hypoventilation is due to the anatomical restriction of the chest bellows rather than to bronchial obstruction and uneven distribution of inspired gas as in emphysema Pulmonary hypertension develops after years of this chronic hypoventilation, at first during exercise and finally at rest.

More recently these observations have been extended (Bergofsky, Turino, and Fishman, 1959) to show that the cardiorespiratory failure in kyphoscoliosis stems from an unusual pattern of breathing, which causes hypoventilation, but which operates to minimize the work and energy cost of mobilizing the deformed chest.

Our own observations support those of Fishman and his colleagues though we have found an occasional patient with emphysema of some parts of the lungs with collapse of the remainder, in the areas compressed by the distorted thoracic cage. Such areas of collapsed lung with continuing blood flow would increase the hypoxia, and their removal, in the few selected cases in which they are found, might be considered in an effort to slow the onset of right heart failure. This and oxygen therapy with stimulation of ventilation, mechanically or chemically, seems the only treatment, apart from that of the heart failure

The dangers of sedatives which depress respiration in such patients cannot be over emphasized. Morphine, even in minute doses, is often lethal Great care has to be taken in procedures such as bronchography · only one side should be examined on any occasion, and sedatives must be avoided

Some patients with kyphoscoliosis have been reported as getting syncopal attacks (Chapman *et al*, 1939) which may be caused by a fall in right atrial pressure following compression of the inferior vena cava when the deformed spine is moved into certain positions.

Extreme Obesity

There are a few extremely obese patients who develop cor pulmonale secondary to chronic hypoventilation, who have automatically normal lungs and whose lung function returns to normal simply by weight reduction. The first analytical investigation of this syndrome was made by Sieker *et al* (1955) It was called the "Pickwickian Syndrome" (a name by which it is often now known) by Burwell (1956) who made further detailed studies of it. The patients are exceedingly obese and tend [illegible] by, their breathing is rapid and shallow with a tendency to [illegible] pal attacks; their arterial blood shows hyp[illegible] ith a hypercapnia associated wit[illegible] the degree of hypoxia produced fr[illegible] polycythaemic, their radiograph shows large pulmona[illegible] and they eventually may develop ankle oedema and a raised jugular v[illegible] pressure from cor pulmonale

Tests of lung function show no defects of intrapulmonary gas mixing or diffusing capacity and parenchymatous lung disease can be eliminated as an explanation of their state in the "pure" obesity syndrome Others show accompanying changes in the lungs themselves (Bedell *et al.*, 1958, Gotsch and Petersen, 1958) The vital capacity is reduced with a markedly lowered expiratory reserve volume The maximum breathing

capacity is corresondingly reduced. The case described by Burwell and others, was a ma of 5 ft. 5 in weighing 121 kg.; his M.B.C. rose from 41 to 133 litres/min, his arteria oxygen saturation rose from 80 per cent to 98 per cent and his arterial P_{CO_2} fell from 7 to 37 mm. Hg after weight reduction to 103 kg., and his associated heart failure disappeared

Pectus Excavatum

This condition, popularly called funnel chest, is not truly comparable with the othe chest-wall abnormalities which cause hypoventilation, for it only very rarely does so Its effect on the circulation is more usually to produce a direct cardiac embarrassmen from antero-posterior restriction of the heart and compression of the right atrium by the sternum In cases of pectus excavatum, biopsy specimens from the anterior part of the diaphragm show poorly developed muscle with much fibrous tissue. During childhood paradoxical movement of the lower sternum is seen which disappears if the phrenic nerve is blocked in the neck.

There are three well-defined clinical types: a localized dent at the lower sternum with steep margins as if a fist had been pushed in the chest, a more diffuse concavity with gently sloping sides, and finally a condition associated with asymmetrical rotation of the sternum usually to the right. The first is the most common.

Symptoms early in life are usually either psychological from the distressing cosmetic effect or they follow repeated chest infections Later in life, from about 25 years onwards, cardiac symptoms from the poor filling of the right auricle may develop and include exertion dyspnoea, pain on exertion and syncopal attacks Occasionally attacks of paroxysmal flutter occur from right atrial pressure stimulation. Surgical correction of the deformity is desirable and the results are good in the first type, reasonably good in the third but rather less satisfactory in the second. Surgery is always justified for cosmetic reasons and if the cardiac symptoms develop in later life, it may become essential (Chin and Adler, 1954, Chin and Duchesne, 1955).

Restrictive Pleuritis

Sometimes gross pleural thickening, such as that seen after empyemata, tuberculosis, etc. (Savage and Fleming, 1955), may in later life give rise to the syndrome of hypoventilation which leads on to cor pulmonale We have seen one such patient, in respiratory failure, in whom the clinical diagnosis on all the usually accepted criteria was of "respiratory failure and cor pulmonale from bronchitis and emphysema" who showed no anatomical emphysema at all at autopsy, but gross pleural thickening and bronchitis

INTERSTITIAL FIBROSIS

There are a number of chronic diseases, of widely differing aetiology which may produce a diffuse interstitial fibrosis in the lungs and with it a remarkably constant and characteristic functional defect of "alveolar-capillary block" (Austrian *et al.*, 1951; Donald *et al.*, 1952) Consequently, the clinical features of the lung disease are similar in all of them so it is convenient to consider them together. They may affect the pulmonary

circulation by causing pulmonary hypertension and cor pulmonale, though these circulatory effects are not common and only occur in a small proportion of cases. The diseases which may cause this characteristic functional change in the lungs are: sarcoidosis, generalized sclerosis (scleroderma), asbestosis, chronic berylliosis, diffuse interstitial pulmonary fibrosis of unknown cause, xanthomatosis including "eosinophilic lung" and other related conditions, diffuse carcinomatosis, microlithiasis and post X-irradiation fibrosis of the lungs.

Functional pathology. The characteristic feature is an increase in the physical barrier to diffusion of gases between alveolar gas and capillary blood ("alveolar-capillary block") due to proliferation of the interstitial connective tissue between alveoli and to change in the alveolar walls. This increased barrier to diffusion principally affects oxygen transfer since carbon dioxide diffuses about twenty-five times as readily as oxygen. Thus there is hypoxia which becomes severe on exercise and then causes cyanosis, without carbon dioxide retention. The exercise hypoxia stimulates breathing and there is a marked increase in exercise ventilation and a low carbon dioxide tension.

Usually the vital capacity is reduced associated with a particular reduction of inspiratory capacity. There is, however, usually no increased airways resistance so that the F.E.V.$_{1\cdot0}$ remains a high percentage of the V.C. and the maximum breathing capacity is relatively little reduced. In some cases the lung compliance may be markedly diminished.

The diffusion difficulty is strikingly demonstrated by measuring the alveolar to end-capillary gradient for oxygen which is increased above the normal 5 to 10 mm. Hg to as much as 30–50 mm. Hg in severe cases; for clinical purposes the most useful diagnostic test is to measure the uptake of carbon monoxide which, expressed as the percentage removal of this gas or as the "diffusing capacity", is found to be markedly lowered Some of these patients have definite inequality of ventilation and of ventilation-perfusion ratios in the lungs (Read and Williams, 1959), but the characteristic changes in lung function tests are the low diffusing capacity and exercise hyperventilation with hypoxia, together with a low inspiratory capacity and high F.E.V $_{1\cdot0}$ compared with the vital capacity. This combination of changes is virtually pathognomic and generally easily distinguished from changes caused by emphysema, asthma, bronchitis, etc.

Clinical features. The main symptom is exercise dyspnoea. Since this occurs early and before definite radiological changes are necessarily present the patient may well be thought to be neurotic unless the appropriate lung function tests are done The characteristic signs are clubbing of the fingers and on listening to the chest fine râles without wheeze. The clubbing occurs early in most cases and may become gross. The râles are initially heard only at the end of inspiration and over the lung margins, later they are widespread, loud and occupy all the inspiratory phase of breathing. The radiographic changes depend on the causal process, and in some of these diseases are fairly characteristic; in others there is a non-specific widespread reticular mottling. The following points can be added about some of the different individual diseases in relation to the changes in the lungs.

Sarcoidosis. This disease, which produces widespread granulomatous lesions in various sites, may affect the lungs either by causing enlargement of the mediastinal glands alone or by producing diffuse parenchymal lesions. The radiographic features in the lungs are correspondingly variable (Garland, 1947). The diagnosis may be very difficult and the

prognosis is very variable (Scadding, 1950; Longcope and Freiman 1952; James *et al.*, 1956). A study of the changes in lung function is different types of pulmonary sarcoidosis (Marshall *et al.*, 1958) showed them to be typical of this group of diseases though there was no close relation between the functional change and radiographic appearance. Function may remain impaired when there is clearing of abnormal shadows on the radiograph. Ventilation, diffusion and compliance changes occur, as in other interstitial fibroses, though the diffusion defect appears the most frequent and the compliance change least often found Many patients improve or recover, other long-standing cases die from intercurrent infection or from lesions elsewhere (such as those of the kidney) so that definite changes in the pulmonary circulation are confined to the few long-standing cases with diffuse lung lesions.

Asbestosis. This condition produces the changes in lung function typical of alveolar-capillary block (Bastenier *et al.*, 1955) and so, with the exception of the rare chronic



FIG 131 Radiograph showing the characteristic features of asbestosis Some patients have advanced clinical and functional changes compatible with interstitial fibrosis of the lungs, together with a long history of exposure to asbestos, yet do not show characteristic changes in their chest radiographs

berylliosis, is unlike other pneumoconioses. The radiographic appearances of some cases of asbestosis are highly characteristic, with a reticular pattern primarily affecting the lower part of the lung fields, a shaggy appearance of the heart border and diaphragm, and pleural thickening (Fig 131). Other cases with undoubted and advanced disease (diagnosed on the basis of industrial exposure, the presence of gross clubbing and râles in the chest and the typical changes in the lung function) show non-specific radiological changes There is evidence that the lowered diffusing capacity, together with clubbing and râles, often precedes radiological signs and that the clinical features and changes in lung function combined with a history of exposure may form a more certain basis of diagnosis than the radiograph (Williams and Hugh-Jones, 1960a and b). Many cases die from carcinoma of the lung which is very frequent in asbestosis, and it has been found that men with asbestosis have about ten times the chance of death from lung cancer as the general population (Doll, 1955). Others get either tuberculosis or bronchiectasis, which is another feature of the disease. Thus, cor pulmonale has not very often been found in asbestosis though it is possible it has become more common since the introduction of antibiotics

Diffuse interstitial fibrosis. The original syndrome of unknown aetiology described

by Hamman and Rich (1935, 1944) was of acute onset and course in middle age There are other similar but chronic examples of diffuse interstitial fibrosis of unknown origin, which may or may not be part of the same process, but which are often called "Hamman-Rich syndrome". They produce functional changes and clinical features typical of this group of interstitial fibroses, and a hyperkinetic circulation with cor pulmonale develops in many, as in the case described by Sloper and Williams (1955). Some get acute exacerbations, apparently not necessarily associated with infection and which are improved by steroids, and during these episodes right heart failure is often manifest This often goes again during a remission of the disease. Few cases survive more than five to ten years after the initial onset The diagnosis is made from the radiographic mottling associated with clubbing, râles and often a persistent cough, and the characteristic functional changes —all without any obvious cause.

Microlithiasis. This rare condition, which has such remarkable radiographic features is reviewed by Sosman *et al.* (1957). Functionally the changes are typical of the group of interstitial fibroses (Thomson, 1959) though the patients may often appear remarkably well considering the gross radiological abnormality. Nine out of fifteen reported deaths from this condition have been due to right heart failure.

"*Honeycomb lungs*." There is a form of cystic lung disease in which there are numerous, widespread, small cavities, usually diffuse but occasionally focal which gives the lung section at post-mortem examination, and the radiograph in life, a fine honeycomb appearance. Oswald and Parkinson (1949) reviewed 16 cases and found six to be associated with generalized disease (xanthomatosis or tuberous sclerosis) while the remaining ten were an isolated manifestation of uncertain aetiology. Heppleston (1956) has since reviewed the pathology in 66 cases and summarized the literature about the condition.

Most cases represent a patchy interstitial fibrosis or granulomatosis blocking some bronchioles but leaving the remainder The underlying process is diverse In infants reticulosis may cause the condition (Mallory, 1942), but most examples in adults are caused by xanthomatosis and the lung lesions can be associated with eosinophilic granulomata or lipoid storage in other organs such as bones or pituitary. The three conditions of eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siewe disease are all related and all may be associated with lung changes. Occasionally these lung changes are also associated with diabetes insipidus though one case of honeycomb lung and diabetes insipidus arose from sarcoidosis (Spillane, 1952) The functional lesion in the lungs is usually typical of alveolar-capillary block. In most of them there is a frequent occurrence of spontaneous pneumothorax Those surviving this hazard usually succumb from right heart failure.

CARCINOMA OF THE LUNG

Primary carcinoma of the lung which is now so common produces relatively little disturbance in the pulmonary circulation except its obliteration where the lung is defective, and sometimes an increased flow in the neighbourhood of the tumour It is claimed that these effects can cause local alteration in the capillary pulsation, found by measuring the intensity of illumination on the fluorescent screen, and so aid the early diagnosis of lung cancer (Kourilsky and Marchal, 1956)

Diffuse pulmonary carcinomatosis secondary to cancer elsewhere does however occasionally give rise to cor pulmonale with pulmonary hypertension (Storstein, 1951). It was initially thought that in such cases the hypertension was the result of thrombo-embolic carcinomatosis but Harold (1952) reviewed the subject, presented 24 new cases, and showed that the cor pulmonale was associated with the alveolar-capillary block described above, and caused by interstitial fibrosis secondary to the distension of peri-bronchial and perivascular lymphatics by tumour cells.

LOCAL OBLITERATION OF THE CIRCULATION

We have been mainly concerned, till now, with the effects of chronic lung disease causing hypertension of the pulmonary circulation and right heart failure As well as this many chronic and locally destructive lesions in the lung, whether they be neoplastic or inflammatory (such as tuberculosis, bronchiectasis, etc.) may, of course, produce localized obliteration of the pulmonary circulation where the lung itself is destroyed. But apart from this, there are chronic lung diseases which produce obliteration especially in the bronchial circulation, and others which obliterate large areas of the true pulmonary circulation, often in an entire lung, without destroying the lung

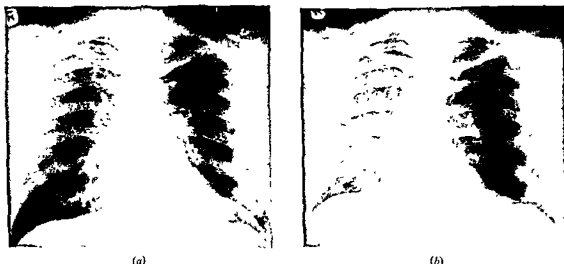
Bronchial Circulation

Any of the diffuse collagen diseases such as polyarteritis nodosa, diffuse lupus erythematosus, rheumatoid arthritis, etc., may produce pulmonary changes; and a review of the literature about them (Ellman and Cudkowicz, 1954) suggests that their pulmonary manifestations are explained by their causing a localized but progressive ischaemia of the lungs from obliteration of the bronchial arterial supply. By contrast, when there is chronic lung disease obliterating much of the pulmonary vasculature itself there may be quite extensive collateral blood flow with the bronchial circulation. Fishman *et al* (1958) found the "*effective*" collateral flow (*i.e.* the component of the total collateral flow reaching the alveolar-capillary surface of the lung and estimated by gas exchange methods) to be about eight per cent of the total pulmonary blood flow in subjects with extensive bronchiectasis, cystic disease of the lung, etc.

Unilateral Obliteration of Pulmonary Flow

In 1954, Macleod described nine patients, all of whom had diminished breath sounds over one side of the chest with abnormal transradiancy of the underlying lung. There was neither obstruction to the main bronchi nor bullous emphysema of the lung, and bronchiographic and bronchoscopic findings on the affected side were essentially normal. Some of these patients have subsequently been further investigated (Dornhorst *et al*, 1957), and the findings in them and in a number of other similar cases studied by different observers show that on the affected side both the ventilation and the pulmonary blood flow are grossly diminished. It is convenient to refer to the condition simply as "Macleod's syndrome" because its underlying pathology is not yet fully elucidated.

Macleod's syndrome is usually readily diagnosed from its distinctive clinico-radiological features, though its differential diagnosis from other causes of unilateral transradiancy of one lung is important. The latter include mainly the following conditions: (1) Complete collapse of an upper lobe (to give only a linear shadow on the radiograph at the lung apex) or, alternatively, complete collapse of a lower lobe (which will be behind the heart shadow on the left side) so that the remaining lobe is expanded, more radiotranslucent than the lung on the other side, and appears to fill the hemithorax like the complete lung. But the breath sounds and bronchographic or bronchoscopic findings establish the true diagnosis. (2) Unilateral emphysema which may be associated with an abnormal bronchogram (Swyer and James, 1953), or with absence of cartilaginous ring to the bronchial tree on one side (Ferguson and Neuhauser, 1944), or with obstruction



(a) (b)

Fig 132a and b. Radiographs from a patient with abnormal transradiancy of the left lung from Macleod's syndrome (a) Inspiration, (b) Expiration

to one of the main branches of the bronchial tree from neoplasms, enlarged glands, etc, or from mucosal flaps (Robertson and James, 1951) In Macleod's syndrome the bronchial tree appears virtually normal on bronchoscopy and bronchography (3) Congenital hypoplasia or absence of the pulmonary vasculature on one side (Madoff *et al*, 1952), where the ventilation is normal on the affected side (as observed clinically and with bronchospirometry) (Belcher *et al.*, 1959), and the loss of pulmonary blood flow is primary and
truction to a pulmonary artery
1959)
...lation and blood flow without obvious cause, may affect the whole of one lung or a similar condition may be confined to one lobe. Recent studies of patients representing both types showed that the affected lung or part of the lung tended to remain inflated during expiration with consequent mediastinal shift to the normal side (Figs 132a and 132b) Detailed investigations have been done in these patients in order to try and understand the condition and its treatment,

Diffuse pulmonary carcinomatosis secondary to cancer elsewhere does however occasionally give rise to cor pulmonale with pulmonary hypertension (Storstein, 1951). It was initially thought that in such cases the hypertension was the result of thrombo-embolic carcinomatosis but Harold (1952) reviewed the subject, presented 24 new cases, and showed that the cor pulmonale was associated with the alveolar-capillary block described above, and caused by interstitial fibrosis secondary to the distension of peri-bronchial and perivascular lymphatics by tumour cells.

LOCAL OBLITERATION OF THE CIRCULATION

We have been mainly concerned, till now, with the effects of chronic lung disease causing hypertension of the pulmonary circulation and right heart failure As well as this many chronic and locally destructive lesions in the lung, whether they be neoplastic or inflammatory (such as tuberculosis, bronchiectasis, etc.) may, of course, produce localized obliteration of the pulmonary circulation where the lung itself is destroyed But apart from this, there are chronic lung diseases which produce obliteration especially in the bronchial circulation, and others which obliterate large areas of the true pulmonary circulation, often in an entire lung, without destroying the lung.

Bronchial Circulation

Any of the diffuse collagen diseases such as polyarteritis nodosa, diffuse lupus erythematosus, rheumatoid arthritis, etc., may produce pulmonary changes; and a review of the literature about them (Ellman and Cudkowicz, 1954) suggests that their pulmonary manifestations are explained by their causing a localized but progressive ischaemia of the lungs from obliteration of the bronchial arterial supply. By contrast, when there is chronic lung disease obliterating much of the pulmonary vasculature itself there may be quite extensive collateral blood flow with the bronchial circulation. Fishman *et al.* (1958) found the "*effective*" collateral flow (*i e* the component of the total collateral flow reaching the alveolar-capillary surface of the lung and estimated by gas exchange methods) to be about eight per cent of the total pulmonary blood flow in subjects with extensive bronchiectasis, cystic disease of the lung, etc.

Unilateral Obliteration of Pulmonary Flow

In 1954, Macleod described nine patients, all of whom had diminished breath sounds over one side of the chest with abnormal transradiancy of the underlying lung There was neither obstruction to the main bronchi nor bullous emphysema of the lung, and bronchiographic and bronchoscopic findings on the affected side were *essentially normal*. Some of these patients have subsequently been further investigated (Dornhorst *et al*, 1957), and the findings in them and in a number of other similar cases studied by different observers show that on the affected side both the ventilation and the pulmonary blood flow are grossly diminished. It is convenient to refer to the condition simply as "Macleod's syndrome" because its underlying pathology is not yet fully elucidated.

inert and harmless space-filling portion of the thoracic contents. Only if it can be clearly demonstrated that the affected part, by remaining inflated during expiration, is mechanically hindering air-flow from the remaining normal lung should removal be undertaken.

Whether the lack of blood flow is consequent upon the lack of ventilation in the lung in this condition, or whether both ventilation and blood flow are both primarily affected by the pathological change, is not really known. In fact the site of the air-trapping, and the cause of the diminished pulmonary circulation through apparently normally developed vessels, remain to be found.

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by the technique of using the radio-isotope oxygen-15 which has only a two-minute half life (Dyson *et al.*, 1958; 1960). In this technique pairs of scintillation counters are placed opposite each other on the chest wall in front and behind, and are used to count the radio-activity from cores of lung tissue between the counters after the patient takes a deep breath of air containing a minute trace of the isotope, and then holds his breath for a short time. The initial activity recorded is a measure of the relative ventilation in the core of lung tissue while the decrease in activity during breath-holding, mainly caused by the removal of oxygen-15 by the blood, gives a measure of the local blood flow The activity

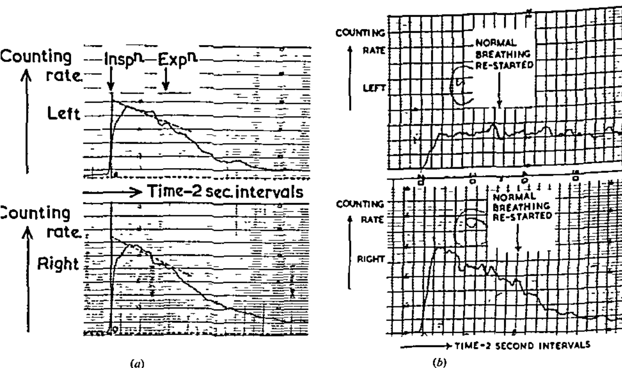


FIG. 133a and b Oxygen-15 recordings, using co-incidence counting, from a normal subject (*a*), and the patient (*b*) with unilateral transradiancy of the left lung from Macleod's syndrome.

then rapidly decreases as the isotope is washed out by subsequent breaths of normal air (Fig. 133a). Typical results in the patient with Macleod's syndrome (Fig 133b) show the diminished ventilation over the affected part of the lung with virtually absent clearance caused by the diminished blood flow. Just as surprising is the persistence of activity in the affected lung during subsequent normal breaths of ordinary air. Other studies show that the affected lung tends to have a valve-like action so that air enters only at the end of a deep inspiration but not during shallow breaths, and is readily "trapped" in it.

Many patients with the condition are entirely symptom-free and the diagnosis is only established after incidental radiology. When the condition is advanced it may be associated with exertional dyspnoea and difficulty with expiration. There seems no reason whatever for treatment in the symptom-free patients, and in them operative removal of the affected lung or lobe in not indicated since it has little air or blood flow and serves as an

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Chapter 13

PULMONARY VASCULAR OBSTRUCTION. LEFT VENTRICULAR FAILURE

By RAYMOND DALEY

THROMBO-EMBOLISM

Emboli which lodge in the pulmonary arteries may be composed of thrombus, tumour fragments, air, fat or amniotic fluid.

Aetiology. The embolic source is most commonly in the deep calf and foot veins but the pelvic veins are sometimes thrombosed after operations on pelvic viscera

Thrombus formation in the calf veins can occur at any time but especially when the velocity of blood flow is reduced. During the 1939–45 war there were a number of sudden deaths due to pulmonary embolism in Londoners who spent the nights in air-raid shelters sitting in deck-chairs with the front bar occluding the popliteal veins. There is little doubt that stagnation of flow does play a part and it is of interest that thromboses after thyroidectomy for thyrotoxicosis are very rare. However, it has often been shown that, if two ligatures are placed on a vein a little distance apart, the blood between them remains fluid. Other factors must be concerned in post-operative thromboses and altered states of blood coagulation have been found Among these there is first an increase in circulating thrombokinase, more being liberated by big operations and more by bilaterial hernia than by unilateral repairs, and secondly, there is an increase in platelet adhesiveness, reaching its maximum eight to ten days after operation.

When a pulmonary embolus occurs without an obvious embolic source it may be that the whole thrombus has been dislodged to form the embolus or that it arises from the right atrium Right atrial thrombi form as often as left and 90 per cent of patients who develop thrombi have chronic atrial fibrillation of over a year's duration Thrombi form slightly more often in the main body of the atrium than in the appendage.

Prophylaxis. During the last war there was a great revival in the enthusiastic treatment of leg vein thromboses Femoral vein ligation under local anaesthesia was commonplace before major surgery, and even in medical wards in patients with heart failure and decreased velocity of blood flow. Large numbers of patients were given prophylactic anticoagulants, and leg exercises became a routine

Since then enthusiasm has given way to balanced thought and a more rational approach.

It has been shown by radioactive sodium techniques that the best way of increasing the speed of flow in leg veins is by repeated extensor and plantar flexion of the feet. It is an advantage if this can be supplemented by daily leg exercises conducted by a physiotherapist.

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arranging them so that the circulation to the cephlic structures, including the central nervous system, was preserved. At any time the cephalic circulation could be interrupted. When the lungs were embolized with small quantities of barium sulphate they found that distension of the right cardiac chambers and increased pulmonary vascular resistance could be greatly reduced when the cephalic circulation was eliminated

Daley *et al.* (1951) using lycopodium spores as the experimental embolizing agent, could find no evidence for reflex vasoconstriction. The increase in pulmonary vascular resistance was comparable whether dogs had an upper dorsal sympathectomy from the first dorsal ganglia to the eighth inclusive, or not. Similarly ganglionic blocking agents or anterior rhizotomy did not alter the response. In a separate series of experiments a catheter was introduced into a lower lobe pulmonary artery, the thorax was opened, and a loose ligature placed round the containing artery Embolization of that isolated lobe had no effect on the vascular resistance of the remainder of the lungs Therefore, as far as anaesthetized dogs are concerned, there is no reflex pulmonary vasoconstriction.

In man a pulmonary embolus has to occlude the main pulmonary artery in order to cause death, provided that the initial lung blood volume is not increased When heart disease is already present, as in mitral stenosis, a small embolus may be sufficient to lead to a fatal increase in vascular resistance

From all the evidence it appears that if any reflex vasoconstrictive mechanism does exist in man it is probably not important. The practical application of this is that any form of ganglionic blocking procedure will not only have little effect on pulmonary haemodynamics but will jeopardize the life of the patient by further lowering systemic pressure.

There are only two known reflex nervous responses associated with pulmonary embolism and these are dyspnoea and the "call for the bedpan". Both are mediated by the vagus. Dyspnoea is abolished by vagal section in the lower cervical region of anaesthetized dogs and if the vagi are cut before experimental embolization has been carried out dyspnoea is prevented The desire to defaecate probably occurs when the pulmonary artery pressure is rising and defaecation in experimental animals happens when the pressure is approximately twice normal; previous vagal section leaves a clean experimental preparation.

While dyspnoea is such a feature of pulmonary embolism it is sometimes accompanied by pulmonary oedema which may cause diagnostic confusion. In man such oedema will only occur when the right ventricular output is maintained. This is unusual and depends upon the integrity of right ventricular function. If, then, a normal cardiac output is perfused through a lung with much diminished vascular capacity the limit of capillary wall distensibility may well be reached with resultant capillary transudation. Dyspnoea will add to the difficulty by transmitting increased negative intrapleural pressure to the capillary wall.

Peripheral cyanosis due to peripheral vasoconstriction with a low cardiac output is common. Central cyanosis will occur in the unusual presence of pulmonary oedema just mentioned, but it may sometimes occur in the absence of pulmonary oedema In these circumstances an oxygen tension of peripheral blood as low as 26 mm. Hg has been recorded. The probable explanation for this is the "opening up" of bronchopulmonary anastomoses.

Whether or not pulmonary embolism leads to infarction depends upon the collateral circulation and the size of the embolus. In conditions in which the bronchial circulation

Binding the legs with thick elastic bandages encourages blood flow in the deep calf veins by compression and restriction of flow in the superficial veins.

Prophylactic ligation of femoral veins is now usually only practised before operations when there has been a history of previous pulmonary embolism or there is evidence of an existing deep vein thrombosis. Thromboses in superficial veins are usually associated with trauma or inflammation (so-called thrombophlebitis) and only 15 per cent of these lead to embolism when there is suppurative liquefaction of the clot. The situation is therefore quite different from sterile thrombus formation (phlebothrombosis) in deep veins when the only attachment of the thrombus may be at the distal end.

It is self-evident that tight bands round the legs should be avoided on the operating table; the worst offenders are diathermy and electrocardiographic attachments

In most centres anticoagulants are not given prophylactically in the post-operative period or in patients with heart failure. They are reserved for use when thrombosis is diagnosed.

Diagnosis. The earliest sign of thromboses in the pelvic or calf veins is a small elevation of pulse rate and temperature, the "chart" sign. In deep calf or foot vein thrombosis the involved limb is more dusky than the other. The veins are fuller, and empty slowly when the limb is elevated. The thrombosed leg is warm and there is usually tenderness in the sole of the foot or on squeezing the calf. The calves of many bedridden patients are tender, but when the calf veins are recently thrombosed there is tenderness not only on squeezing *from side to side* but also *from front to back*

The diagnosis of pelvic vein thrombosis is much more difficult and is usually made by inference. There may be low abdominal tenderness or tenderness per rectum.

When a pulmonary embolus has occurred the respiration rate will also increase. There may be pleural pain or haemoptyses. If the embolus is large the jugular venous pressure will rise, the main pulmonary artery may be easily felt, a pulmonary systolic murmur may occur and the pulmonary sound increase in loudness. The involved side of the chest will move less than the other Other lung signs may be absent or there will be signs of consolidation or pleural effusion which is usually haemorrhagic.

Electrocardiographic changes of right ventricular "strain", with tall R waves in the right chest leads and T wave inversion maximal in the antero-septal sites, are normally only present when the venous pressure is raised, (Chapter 7). Radiology is a notoriously disappointing aid to the diagnosis of this condition. There may be no changes at all, especially if the infarct is behind the heart shadow. The changes which do occur vary *from hazy opacification* to discrete shadows of any shape The commonest finding is a pleural effusion Several weeks after an infarction has occurred linear shadows may develop and remain as permanent relics (Chapter 5).

When a pulmonary embolus has lead to infarction jaundice may develop due to red cell destruction and the sedimentation rate and serum transaminase will be raised

Haemodynamics of pulmonary embolism. *There has been much controversy as to* whether pulmonary embolism leads to pulmonary hypertension by pure mechanical blockage or whether there is a reflex vasoconstrictive mechanism. In experimental pulmonary embolism in animals, Daly *et al.* (1948) in a series of meticulous experiments

although the post-operative disability is less than might be supposed, there is commonly residual oedema.

Tumour Embolism

Tumour fragments from any systemic site which is not drained exclusively by the portal veins may gain access to the venous system and travel to the lungs. There is some conflicting evidence as to the particle size which will pass through lung capillaries. Experimentally, smooth glass beads of 300 µ may do this but adhesive spores such as lycopodium will not do so with an average diameter of only 50 µ. Therefore, whether the fragments are of tumour cells or conglomerations of bacteria or other organic material, impaction in the lungs will depend upon the physical properties of the substance.

Many examples of tumour embolism are recorded (Mason, 1940) There is usually secondary thrombosis, and right ventricular failure often precedes death. Occasionally malignant tumours of the lung itself may invade pulmonary arteries and disseminate through one or both lungs.

Brill and Robertson (1937) and Storstein (1951), in discussing right ventricular failure associated with carcinomatous metastases in the lung, point out that, apart from embolism, lymphangitis carcinomatosa may involve small arteries and produce pulmonary hypertension, or engorged lymphatics may compress alveoli and capillaries

McMichael (1948) included chorionepithelioma as one of the causes of embolic subacute pulmonary hypertension, and his case and two others are fully described by Bagshaw and Brooks (1959). The patients presented with dyspnoea and in two there were recurrent small haemoptyses. There was weight loss, central cyanosis, and clinical evidence of pulmonary hypertension.

Embolism from the products of tumour is typified by the *metastasizing carcinoid of the ileum* This tumour produces a substance, 5-hydroxytryptamine, in the liver and in mesenteric secondary deposits, which travels to the lung where it is changed by an unknown chemical mechanism to 5-hydroxyindolacetic acid. The latter can be detected in the urine where its measurement can lead to the diagnosis. The paroxysmal release of 5-hydroxytryptamine causes intermittent pulmonary arteriolar vasoconstriction with considerable liability of pulmonary artery pressure. During periods of increasing pulmonary resistance there is a fall in systemic pressure. The combination of these effects leads to paroxysmal flushing and it is thought that fibrotic changes in the right heart are responsible for narrowing of the tricuspid and pulmonary valves This extraordinary condition was first described by Cassidy (1930) and has recently been extensively studied by Biorck *et al.* (1952) No other substance with an exclusive pulmonary vasoconstrictive action has so far been described

Air Embolism

Large quantities of air can be introduced into the pulmonary circulation without untoward effect provided that the introduction has been slow Thus, in experimental dogs, up to a litre of air can be injected slowly into a systemic vein with the animal lying on the left side. Such positioning has been employed in man after the accidental introduction of air into a vein during transfusion or cardiac catheterization If a sufficient number of pulmonary capillaries are not occluded by air bubbles the patient will live

is well developed infarction is less likely, although if it does occur the infarcted area is likely to be extremely haemorrhagic. Small peripheral emboli occurring in otherwise healthy lungs will normally produce small infarcted areas which ultimately contract to fibrous scars Massive infarction of a whole lung is usually not compatible with life.

Sequelae. If a patient survives a single pulmonary embolus for more than a few hours he is likely to live. Dyspnoea at rest may persist for days or weeks but will gradually diminish. Effort dyspnoea may take up to six or nine months before maximum improvement is obtained As explained by Harrison in Chapter 6 the embolus slowly contracts towards the arterial wall with central recanalization. The lumen, therefore, may be permanently narrowed but adequate to allow sufficient blood flow except during considerable effort. The situation is comparable to that after pneumonectomy when large blood flows cannot be accommodated in the remaining lung without over-distension

Continued deterioration in a patient's condition following a pulmonary embolus suggests that either a thrombus has built up proximal to the embolus or that further emboli have lodged. The latter is more common and causes the clinical picture known as "packed pulmonary embolism". Usually a series of small emboli seal off a progressive number of pulmonary artery branches causing increasing pulmonary hypertension and dyspnoea This sequence of events accounts for a number of unexplained forms of pulmonary hypertension but is probably too often invoked as an explanation of the aetiology of primary pulmonary hypertension (see below).

Treatment. Surgical removal of serious pulmonary emboli by the Trendelenburg method has proved very disappointing as there is usually so little time available before the patient expires. However, Crafoord has successfully performed the operation on several occasions In the future surgery may well be feasible in patients who survive the initial attack. Removal of the embolus with or without the containing artery and using a graft, or using some form of "thrombectomy" operation may be tried. The difficulty, as compared with similar procedures employed in the systemic circuit, is the relatively low intra-arterial pressure with subsequent liability to thrombus formation.

Medical treatment comprises morphia, oxygen and anticoagulants Morphia constricts the systemic circulation and has some unknown favourable effect on the respiratory centre In the absence of pulmonary oedema, when the advantages of oxygen therapy are clear, oxygen can only help by increasing the plasma oxygen tension and by adding the very small increment from normal to full arterial oxygen saturation. Anticoagulant therapy is best begun with intravenous heparin, which is either continued intramuscularly or replaced by a synthetic oral anticoagulant. Anticoagulants should be continued until the patient has been mobile for several days, usually a period of two to three weeks being necessary. Mobilization should take place gradually from bed Sitting in a chair with kinked leg veins should be avoided.

Ligation of veins is indicated when further emboli have occurred despite adequate anticoagulation, or when there are contra-indications to the use of anticoagulants such as a history of peptic ulcer or haemorrhagic disease If there are unequivocal signs of thrombosis of the calf veins femoral vein ligation is usually sufficient. If the femoral veins are thrombosed, ligation of the internal iliac veins is nowadays usually favoured rather than ligation of the inferior vena cava. The last is reserved for pelvic vein thrombosis because,

Amniotic Fluid Embolism

Steiner and Lushbough in 1941 first described maternal pulmonary embolism by amniotic fluid. Since then there have been several reports on this rare complication.

The patients are usually multiparous and in their late thirties or early forties. The pregnancy is usually uneventful, but shortly after labour starts there is sudden dyspnoea, cyanosis and shock. Death usually occurs in minutes or hours. Amniotic fluid enters the maternal circulation via uterine sinusoids and is thought to do so because of strong uterine contractions occuring when a large baby obstructs the lower end of the uterus The clinical picture may be due to mechanical obstruction of the pulmonary vessels but this seems a little unlikely as in some patients the fluid has clearly passed through the lungs and is demonstrable in the left heart and kidneys. It seems more likely that there is an anaphylactoid reaction associated with thrombi in the pulmonary arteries. It is also thought that the thrombi use up quantities of fibrinogen which is responsible for the bleeding which often accompanies this condition. Such bleeding may occur from the mouth, uterus or lungs, and purpura has been reported. Treatment can only be directed towards increasing the coagulability of blood Reid *et al.* (1953) had reasonable success using fibrinogen replacement therapy and blood transfusion. Four of their five patients recovered

IDIOPATHIC PULMONARY HYPERTENSION

Wade and Ball (1957) believe that there are at least three mechanisms concerned in the production of idiopathic pulmonary hypertension

(1) functional narrowing of muscular vessels with or without thrombotic occlusions;
(2) primary pulmonary arteritis; and
(3) bronchial and pulmonary communications through abnormal vessels, resulting in a dynamic state analagous to that of persistent ductus arteriosus.

There are also occasional patients who die from right heart failure without histological changes in the pulmonary vessels, as if from essential pulmonary hypertension.

The disease is more common in women and, while it may occur at any age, it usually develops in the late teens or early twenties. The presenting symptom is dyspnoea of effort It differs from dyspnoea from other causes in that the patient can walk a moderate distance without difficulty but is then suddenly seized by a feeling of suffocation. The cardiac output is low and there is little or no ability to increase it with effort. Hence there is inadequate coronary blood flow, and right ventricular angina is a common symptom. Effort syncope often occurs and the mechanism is probably twofold First, there is acute right ventricular failure causing an even further reduction in cardiac output, and secondly, systemic vasodilatation during effort leads to pooling of blood and diminished cerebral perfusion. The last was dramatically seen in a patient who became blind a few seconds before she became unconscious, and this was accompanied by extreme retinal blanching.

The signs are: low blood pressure; a prominent venous "a" wave; a right ventricular heave with a palpable pulmonary artery; the pulmonary sound is loud and there is closed splitting of the second sound. Central cyanosis is usual with an arterial oxygen saturation

Fat Embolism

Fat embolism in the lungs classically occurs after accidents causing bone fracture when marrow fat enters the blood stream. It may, however, occur after a variety of other accidents in which bones are not broken

Fat globules have to be of higher diameter than 12 μ in order to obstruct pulmonary capillaries It is probable that this is why diseases with very high blood lipids, such as diabetic coma, do not cause lung lesions (Harris *et al.*, 1939). Experimentally, hydrolysed fat is more toxic than neutral fat and Taquini *et al.* (1956) have calculated that approximately 5 c.c. would prove lethal to man In order to explain the delay of hours, or even a few days, between trauma and the onset of symptoms it is believed that there is slow liberation of fatty acids. Robb-Smith (1941) found that in 789 consecutive accident cases 125 died and of these 41 had gross pulmonary fat embolism At post-mortem, lungs cleared with potassium hydroxide display fat in the alveolar capillaries as refractile clusters or cylinders with a narrow dark edge.

After the initial asymptomatic period there develop sweating, dyspnoea, and profuse expectoration of a pink fluid in which fat may be found. There is little cough There is pleural pain and there may be symptoms of fat embolism elsewhere, such as in the brain and kidneys, and purpura is common. Pulmonary oedema causes central cyanosis and there is surprisingly little drop in systemic pressure in view of the pulmonary vascular obstruction The chest X-ray merely shows the pattern of pulmonary oedema

Taquini *et al.* (1956) fully investigated a patient suffering from lung fat embolism following therapeutic injections of thymol in oil. They attributed the marked hyperventilation to stimulation of stretch receptors by increased lung rigidity and to stimulation of chemoreceptors due to anoxaemia. The arterial oxygen saturation was 55 per cent when breathing air but could be increased to normal with oxygen breathing The pulmonary artery pressure was 55/22 mm Hg and the cardiac index 6 35.

Prophylaxis involves early immobilization of injured parts, and when symptoms have developed, oxygen therapy and other treatment for pulmonary oedema are used. It is probably rational to give steroids in the hope of inhibiting pulmonary exudative reaction to the irritant.

Thrombosis of the Pulmonary Arteries

Thrombosis of the main pulmonary artery is rare as a primary event, although retrograde thrombosis following pulmonary embolism is quite common It is more likely to occur when there is pulmonary atheroma or, rather strangely, when there is increased pulmonary blood flow as in auricular septal defect, especially on the right side.

There is a sudden onset of dyspnoea associated with the signs of pulmonary hypertension. The diagnosis is suggested radiologically by seeing either main pulmonary artery to be excessively wide and opaque, with the distal lung appearing hypertranslucent [illegible] than the left The prog- [illegible] arent- [illegible] dition too readily and at times the passage of a cardiac catheter through the supposedly thrombosed artery has been a salutary procedure

OBSTRUCTION TO LEFT VENTRICULAR FILLING

Obstruction to left ventricular filling due either to left ventricular failure or diminished capacity of the left ventricle will cause pulmonary venous hypertension.

Left ventricular Failure

Whatever the cause of left ventricular failure the haemodynamic effect is the same, that is, the end-diastolic (filling) pressure is raised. There may be a residual volume of blood in the ventricle at the end of systole, but as the forward output falls there is still a residuum of pressure at the end of diastole requiring an increased filling pressure from the left atrium. [illegible]

probable that there is "active" pulmonary arteriolar vasoconstriction. There is considerable evidence in other circumstances that a rising left atrial pressure leads to a rise in pulmonary arteriolar resistance. Calazel *et al.* (1951) have shown this to be true in atrial septal defects and its occurrence in mitral stenosis is generally accepted. The radiological changes of left ventricular failure resemble those of mitral stenosis (Chapter 5) and may show narrowing of the lower lobe arteries as in mitral disease. The form of the left atrial pulse in left ventricular failure is similar to that in mitral incompetence, which may occur as a result of left ventricular failure. However, pulmonary arteriolar vasoconstriction is unlikely to be so pronounced as in mitral valve disease for the elevation of left atrial pressure is not so chronic or so marked.

Acute left ventricular failure gives rise to pulmonary oedema as in mitral stenosis (see Chapter 8) and, as discussed elsewhere, the more rapid the rise in left atrial pressure the more likely is pulmonary oedema than cardiac asthma to occur. The degree of left ventricular diastolic hypertension in left ventricular failure is not known, but data from left heart catheterization and left ventricular puncture suggest that it may reach levels of 20–30 mm Hg or even higher, which would entail a left atrial pressure of at least 25–35 mm Hg.

The effects on pulmonary function are similar to those in mitral stenosis, with undue rigidity of the lungs and a necessity for increased work to produce ventilation.

The symptoms of left ventricular failure comprise exertional dyspnoea, orthopnoea, nocturnal dyspnoea and attacks of pulmonary oedema The physical signs are those of left ventricular enlargement as judged by the quality and position of the apex beat and lateral chest sway, presystolic or diastolic triple rhythm, which may be visible and palpable as well as audible, basal pulmonary crepitations and often hyrdothorax. Pulsus alternans may not only be present in the systemic circulation but also in the pulmonary circulation. Unless acute left ventricular failure follows massive cardiac infarction there is usually a rise in systemic pressure. Systemic vasoconstriction following small cardiac infarctions may be so intense that left ventricular failure may be erroneously attributed to hypertension and the error only appreciated when, after the attack, the patient is normotensive. Functional tricuspid insufficiency and secondary right ventricular failure are common.

Breathlessness on exertion is due to the increased work of breathing caused by the turgid, stiff lungs, which contain an increased volume of blood (Kopelman and Lee, 1951).

often less than 90 vols. per cent. There has been much controversy as to the cause of cyanosis but it is probable that a number of pulmonary capillaries by-pass functioning alveoli and shunt blood because of obstruction to the usual arterial channels. Alternatively there may be a right to left shunt through a patent foramen ovale.

The electocardiogram shows considerable right ventricular hypertrophy without a bundle branch block pattern On X-ray the right ventricle and main pulmonary artery are enlarged and there is an abrupt reduction in pulmonary vascular shadows in the periphery of the lung. The diagnosis is confirmed by cardiac catheterization when, in the absence of an intracardiac shunt, there is pulmonary arterial hypertension with a normal pulmonary capillary pressure Angiocardiography is dangerous because it causes even further reduction in adequate blood oxygenation Rose's sheep cell agglutination test is frequently positive in this disease as it is in various collagenoses and some vascular allergies such as polyarteritis nodosa, but the histology in most cases is quite dissimilar from that of polyarteritis (see Chapter 6).

There have been many attempts to reduce pulmonary vascular resistance by drugs. While continous intravenous infusion of acetylcholine may sometimes reduce vascular resistance a little, it is impracticable as therapy. No other drugs have been found to have the same action Ganglionic blocking agents not only have no primary action on pulmonary vasculature but also are dangerous because of their effect in reducing systemic blood pressure. The same remarks apply, to removal of sympathetic ganglia A few attempts have been made to shunt blood from the lungs to the systemic circuit when the pulmonary artery pressure exceeds the systemic on exercise. The creation of such a "reversed" ductus has not been successful and such patients are liable to sudden death at operation just as during cardiac catheterization. Anticoagulants have been advocated (Chapter 4).

DISEASES OF PULMONARY VEINS

Little is known of these conditions Pulmonary veins can, of course, be invaded by bronchial cardinomata or lung abscesses leading to diffuse dissemination of cells or organisms. Otherwise they may be the seat of atheroma or any form of arteritis, especially pulmonary vascular system.
that of mitral stenosis or membrane ob-

Ferencz and Damman (1957) described the case of a child who died, aged two and a half years, with right heart failure and pulmonary hypertension. There was atresia of the vein from the left lower lobe and stenosis of the upper lobe vein of the same side Reyke (1951) reported an eight-year-old girl who died from right heart failure due to stenosis of the veins from the left upper and lower, and the right lower lobes with atresia of the right upper lobe vein. Obstruction of the pulmonary veins at their junction with the left auricle, which may have been a congenital malformation, is described by Bernstein, Nolke and Reed (1959) The clinical course was characterized by haemoptyses probably due to a highly developed collateral bronchial circulation In this instance there were the complicating factors of pulmonary and arterial venous thrombi and hypertensive arteritis.

Radiological changes are not remarkable except for pericardial calcification in constrictive pericarditis and generalized poor pulsation on fluoroscopy. The cardiogram is discussed in Chapter 7.

The differentiation between constrictive pericarditis and endomyocardiomyopathy is often extremely difficult. A history of tuberculosis or pericardial effusion and the finding of pericardial calcification are the most reliable points In the absence of calcification, heart size may be significant, the heart in endomyocardial constriction being usually larger than in constrictive pericarditis. In infancy and childhood endocardial fibro-elastosis is the commonest member of this group of diseases likely to be encountered, and diagnosis will be aided if the process has spread to involve valves, especially the aortic and mitral valves. In adult life the commonest cardiomyopathies are amyloid disease of the heart and eosinophilic cardiomyopathy. It is unfortunately rare to find diagnostically useful facets of these diseases elsewhere in the body.

Treatment

Treatment of constrictive pericarditis is surgical when previous medical treatment has reduced oedema as far as possible. This is achieved in the usual way with diuretics and salt restriction; digitalis should not be used because it causes bradycardia The success of pericardectomy depends upon the ability of the surgeon to remove all the constricting pericardium and upon the degree of myocardial fibrosis However extensive the operation may be, and however much improved the patient may feel, haemodynamic studies never completely return to normal. The prediction of myocardiae fibrosis before operation is not possible but the presence of atrial fibrillation may be suggestive of it.

The treatment of constrictive cardiomyopathy is usually non-specific and disappointing Occasionally steroid therapy is strikingly successful in polyarteritis nodosa, but healing of coronary arterial lesions is too often accompanied by fibrotic occlusions and multiple infarction.

Functional Obstruction of the left Ventricle

It has been recognized for several years that severe hypertrophy of the outflow tract of the right ventricle may develop in conjunction with pulmonary stenosis or ventricular septal defect. After surgical resection of the primary defect, pressure gradients in the vicinity of the hypertrophied area gradually diminish

Brock (1957) reported similar obstruction to left ventricular outflow in patients following successful aortic valvotomy with a gradual decrease in pressure gradient. He also described similar left ventricular hypertrophy with systemic arterial hypertension. Morrow and Braunwald (1959) describe two patients in whom there was a significant pressure gradient in the left ventricular outflow tract, and at open heart operation no localized stenotic area was found They attributed such a systolic pressure gradient to massive muscular hypertrophy of unknown cause. Post-stenotic dilatation of the aorta has not been seen. Left heart catheterization demonstrates obstruction to the outflow of the left ventricle, and its actual level may be seen using selective left ventricular angiocardiography. A similar, though not necessarily identical, condition designated as obstructive cardiomyopathy, which mimics aortic stenosis has been described, by Goodwin *et al* (1960).

Orthopnoea is due to the greater volume of blood in the lungs in the horizontal rather than the verticle position (McMichael, 1947), and to the reduced mechanical advantage of the necessary respiratory muscles in the recumbent position.

Constrictive Cardiomyopathy

The site of restriction to ventricular filling may be in the pericardium and epicardium (constrictive pericarditis) or in the myocardium or endocardium. Wherever the site of the constriction the haemodynamic effects are closely similar.

The ventricles are unable to dilate adequately to receive the inflow of blood from the atria Filling is, therefore, impaired and output correspondingly restricted. The impairment of filling may effect both ventricles equally or one more than the other When both are equally affected despite a rise in atrial pressures, significant pulmonary hypertension does not generally occur because of the restricted output of the right ventricle

The intracardiac pressure pulses show characteristic abnormalities. The mean atrial pressure is raised and the pulse contour shows "a" and "v" waves of equal proportion with sharp "x" and "y" descents. The ventricles fill rapidly in early diastole but the restricting process soon limits further filling and the maximum capacity is reached early with sharp rises in ventricular and atrial pressures. The ventricular pulse shows a typical early diastolic trough coinciding with the sharp "y" descent of the venous pulse After the early diastolic dip the ventricular pressures rise rapidly to a high plateau in late diastole.

On inspiration the caval and pulmonary venous pressures rise owing to the inability of the ventricles to increase stroke volume in response to increased blood flow. It has been suggested that, when the rise in pressure in the pulmonary veins is greater than that in the venae carvae, left ventricular filling may be directly impaired by tension on a rigid pericardium or myocardium when the diaphragm descends. A similar mechanism has been evoked to explain arterial pulsus paradoxus (Wood, 1956), but the alternative explanation that distension of the right ventricle in a rigid pericardial sac interferes with left ventricular filling (Dornhorst and Leathart, 1952) has much to commend it in constrictive pericarditis Usually venous pulsus paradoxus is more common than arterial. Tachycardia is the rule and represents an attempt to maintain forward output in the face of impaired filling; no attempt should be made to reduce the heart rate. The Valsalva manœuvre may give a square wave type of response, as in severe valvular disease and heart failure, with "overshoot" of arterial pressure and bradycardia (Wood, 1956)

The symptoms of constrictive cardiomyopathy are tiredness and swelling of the abdomen. Dyspnoea is not an important feature. The quiet cardiac pulsation is in striking contrast to the high jugular venous pressure and may help to distinguish constrictive cardiomyopathy from cardiac failure of other aetiology The form of the venous pulse separates the constrictive syndrome sharply from tricuspid stenosis, the other cause of a high venous pressure and small quiet heart (see Chapter 4). A loud third sound or summation gallop rhythm may occur in constrictive endomyocardiopathy. A similar third sound is a feature of constrictive pericarditis and the closeness of it to aortic valve closure is a measure of the severity of the constriction (Mounsey, 1955). In severe cases there is ascites, hepatic enlargement and oedema. Atrial fibrillation occurs in about 30 per cent of patients.

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The systolic murmur is maximal at the left sternal edge and the pulse is jerky rather than anacrotic. The signs of obstruction to other parts of the heart may be present due to massive assymetrical hypertrophy.

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Chapter 14

PULMONARY OEDEMA

By RAYMOND DALEY

Acute leakage of blood elements from pulmonary capillaries into alveoli may be due to an excessive pressure gradient across the capillary alveolar "barrier" or loss of integrity of the capillary wall The former is the cause of pulmonary oedema in left ventricular and left atrial failure; it is also the cause of oedema complicating head injuries and other cerebral disturbances such as tumours, infections and vascular accidents. The last only occurs in man after exposure to gases such as chlorine and phosgene although in experimental animals it can be produced by several other chemicals. There are, however, a few diseases causing subacute pulmonary oedema in which there is probably a combination of increased capillary pressure and altered permeability.

Experimental Pulmonary Oedema

The barrier between the lumen of pulmonary capillaries and the lumen of alveoli is about 0 8 μ. It is composed of the capillary wall, interstitial tissue, alveolar lining membrane and a mucin layer. Pulmonary lymphatics drain transudates from this area until they are overloaded, when fluid escapes from the capillaries into the alveoli and causes pulmonary oedema with expectoration of frothy, sometimes blood-stained sputum. If there has been a gradual capillary leakage the "barrier" increases in thickness and cardiac asthma, with acute dyspnoea rather than expectoration, is more likely to occur.

The normal mean pulmonary capillary pressure in man, as measured by the wedged catheter technique, is *5 to 10 mm. Hg. Intrathoracic pressure alterations with respiration* will alter the effective capillary filtration pressures when they are extreme as in hyperventilation or bronchial obstruction.

The normal osmotic pressure of plasma proteins is about 25 mm Hg Hence, theoretic*ally the* capillary pressure has to be increased or the osmotic pressure lowered before, purely on pressure relationships, leakage can occur In fact, cannulated pulmonary lymphatics in animals do contain considerable quantities of protein, and constant minor loss of capillary protein is probable.

In man, pulmonary oedema consequent upon left ventricular or atrial failure results from a rise in pulmonary capillary pressure Less easy to understand is pulmonary oedema complicating cerebral disturbances. Sarnoff and Sarnoff (1952) have thrown considerable light on this They injected fibrin into the cisterna magna of dogs and showed that there was systemic vasoconstriction and presumably venous constriction as the pulmonary blood volume increased So marked was the pulmonary "overload" that the limit of vascular distension was reached, the pulmonary capillary pressure rose and once again capillary

leakage resulted from capillary hypertension. Denervation of the lung did not alter this phenomenon but release of systemic vasoconstriction by ganglionic blocking agents prevented its occurence. In other experiments Sarnoff (1959) has shown that the marked elevation of left atrial pressure during experimental aortic occlusion in the dog is accompanied by increased venous tone; that is, decreased venous distensibility. The distensibility does *not* alter when the experiment is repeated under ganglionic blockade. How far these results can be translated to human experience is unknown but at least venous distensibility, as in other forms of pulmonary oedema, is accompanied by a rise in systemic pressure. Therefore, it is *likely* that pulmonary oedema in most of its human forms is caused by a simple pressure change

Sarnoff, by studying ventricular function curves in which the left atrial mean pressure is plotted against left ventricular stroke work, has also stressed that isolated left ventricular failure can occur If the left ventricle is to produce a near normal stroke volume and aortic pressure, and in order to do this the left atrial pressure (filling pressure) must rise, it follows that the hydrostatic filling pressure may at times well exceed the osmotic pressure of plasma proteins

One of the most interesting drugs used in the production of experimental pulmonary oedema is alphanaphthol thiourea (ANTU) This substance when injected in oily solution into the peritoneal cavity of dogs and rats causes death from pulmonary oedema, and bilateral pleural effusions in six to ten hours. It apparently leads to capillary wall leakage without alteration in pressure. The phenomenon is accompanied by increasing dyspnoea and a rising haematocrit. Autonomic denervation either by dorsal sympathectomy (T1 to T8), vagotomy or the use of ganglionic blocking agents does not prevent oedema and death The situation is therefore very similar to that of "war gas" pulmonary oedema. It has little application to man in that, most fortunately, thiourea-like compounds given by mouth do not cause clinical pulmonary oedema. The sociological application is the use of ANTU as a rat and mouse poison; the hope being that vermin will become so dyspnoeic before death that they will seek open spaces

Several investigators have with difficulty produced pulmonary oedema by increasing pulmonary blood volume using rapid transfusion of hypertonic saline into dogs. Large quantities are required to cause "overload" and such grossly abnormal circumstances probably never occur in man. However, in the presence of existing increased pulmonary blood volume further minor increments of volume can lead to oedema, hence the danger of transfusing rapidly patients with left ventricular failure, and of giving salt-retaining drugs such as oestrogens and steroids.

Haemodynamic changes. Much information about the circulatory changes occurring during attacks of pulmonary oedema has now been obtained by cardiac catherization, especially in patients suffering from mitral stenosis (see Chapter 8). Attacks are precipitated by, for example, recumbency on the X-ray table, anxiety causing systemic vasoconstriction and tachycardia, and exercise tests. The already high pulmonary artery and capillary pressures suddenly increase without an appreciable increase in pulmonary vascular resistance. The systemic pressure rises and the cardiac output usually increases a little. These events are dependent upon maintenance of right ventricular efficiency and hence a climbing jugular venous pressure is not a feature of the attack. As the air passages fill with transudate so the arterial oxygen saturation falls. The direct action of hypoxia causing

pulmonary capillary leakage has probably been over-estimated. By analogy it is certain that anaemia has to be of a very serious degree before capillary wall nutrition suffers

In virtually all forms of human pulmonary oedema it seems that, when the pulmonary capillary pressure exceeds that of plasma protein osmotic pressure, pulmonary oedema will occur. If the discrepancy in pressures is slowly brought about, the pulmonary capillary pressure may rise very high without pulmonary oedema occurring, the transudate being carried away by lymphatics. When the change is sudden a clinical attack of pulmonary oedema occurs Much has been written suggesting that attacks are precipitated by pulmonary venous constriction, the "venous throttle" mechanism, but there is no experimental evidence in support of it.

The immediate precipitating causes of attacks are fairly comprehensible in such diseases as mitral stenosis when there is a sudden increase in heart rate leading to a further rise in left atrial pressure, or the increased work of the heart and increased pulmonary blood volume of recumbency. In left ventricular failure due to systemic hypertension it is likely that nocturnal attacks have, as their cause in addition to the effect of recumbency, sudden increases in venous return and heart rate due to rapid muscular movements.

Dyspnoea in pulmonary oedema is a striking feature and has been attributed by Hayward (1955) to increased lung rigidity due to interstitial transudation. A good indication of lung rigidity is obtained by measuring intrathoracic pressure with an oesophageal catheter. He suggests that lessening of dyspnoea after a successful mitral valvotomy may be due to improved lung distensibility and that during exercise there is no increase in rigidity. These phenomena could follow reduction in pulmonary venous and capillary pressures although cardiac output and pulmonary artery pressure are, at times, little altered He also suggests that other factors increasing lung rigidity in pulmonary oedema are bronchospasm and altered surface tension changes due to the sticky mucinous fluid in the alveoli.

Subacute Pulmonary Oedema

There are a number of conditions associated with prolonged pulmonary oedema in which there is some interstitial oedema, but the main feature is a fibrinous alveolar exudate containing mononuclear cells and fibroblasts. The alveolar ducts are dilated and lined by a hyaline membrane (Doniach, 1947). The lungs are tough and solid in consistency especially in the hilar regions These conditions are uraemia, acute nephritis, polyarteritis nodosa and "rheumatic lung" of acute rheumatism. In all of them the pulmonary capillary pressure is probably raised because of left ventricular failure, but this may not be great and it is likely that there is some loss of capillary wall integrity Certainly, at times, in all these conditions there is increased fragility of systemic capillaries In polyarteritis nodosa involvement of lung blood vessels is accompanied by a blood eosinophilia Rheumatic lung is an uncommon manifestation of acute rheumatism and its existence is even doubted by some. The writer has seen a child with acute rheumatism who developed recurrent dyspnoea and lung opacities when treated with large doses of salicylates and it is tempting to wonder how much lowered plasma prothrombin levels played in the aetiology

Subacute pulmonary oedema has been seen in some patients while under treatment with hexamethonium compounds for systemic hypertension and helps to throw light on

other forms of the condition. In order to produce it the dose of the drugs has to be critical, when it seems that acute pulmonary oedema is avoided, but slow capillary seepage occurs with subsequent intra-alveolar organization of the exudate. Increasing the dose may abolish it.

Clinically there is intense dyspnoea with few or no added sounds to be heard. The lack of clinical signs is in marked contrast to the extensive radiological shadowing

Clinical Aspects of Acute Pulmonary Oedema

The commonest causes of acute pulmonary oedema are mitral stenosis, hypertension, aortic valve disease and cardiac infarction.

Mitral stenosis is fully discussed in Chapter 8 and in general the acute attack differs little from that due to other cuases with the exception of a few small points described below. Attacks may range from inability to walk and talk at the same time, and mild dyspnoea when recumbent, to severe attacks of very sudden onset. In the latter dyspnoea with chest oppression are the dominant early features. Later there is wheezing and peripheral vasoconstriction with a rise in systemic pressure and peripheral cyanosis As the attack proceeds the ventricular rate increases. Sinus rhythm is common unless an acute rise in left atrial pressure has been produced by the onset of a paroxysmal arrythmia with a fast ventricular rate. The attack may subside with or without treatment at this stage or give way to the expectoration of pink, frothy sputum with fine crepitations, especially in the mid and lower zones As the bronchi and alveoli become obstructed with fluid there is intense central cyanosis and death may occur from asphyxia or peripheral circulatory failure.

The association of pregnancy with mitral stenosis produces two of the most dangerous circumstances which can arise in this condition These occur at the onset of labour or immediately after delivery. The emotional situation leads to tachycardia and vasoconstriction; the patient is often lying fairly flat and the uterine "lake" of blood is being transfused into the general maternal circulation. Prophylaxis of these attacks necessitates the prediction during pregnancy of severe mitral stenosis and pulmonary venous hypertension. Valvotomy is then a most reasonable procedure to advise. Otherwise full digitalization, diuresis and venesection of a pint of blood should be carried out before the onset of labour. Recumbency should be avoided and the labour made as easy as possible by suitable episiotomies and the use of low forceps It should be remembered that oxytocic drugs also have an unfavourable vasoconstrictive action. Caesarean section is most inadvisable except for obstetric necessity because of the sudden overload of the maternal circulation by the rapidly contracting uterus. If excessive blood loss has occurred during labour the pint of blood previously removed can be slowly transfused.

In *hypertensive left ventricular failure* there has usually been a previous history of effort dyspnoea before the acute attack of pulmonary oedema. In these patients a rise in systemic pressure precedes the attack for a few minutes and accompanies at least the early stages. Pulsus alternans is common and it is interesting that, in patients who have had a cardiac catheter in the pulmonary artery at the time, it is also demonstrable in the pulmonary artery pulse.

In *aortic valve disease*, especially aortic stenosis, an attack of pulmonary oedema may

be the first indication of disease. It classically occurs in men in their late forties, and if the initial attack is survived the downhill course is almost invariably rapid.

Cardiac infarction may cause pulmonary oedema in three somewhat different circumstances. First, with or without chest pain, there is an acute attack with much frothy sputum. Secondly, six to eight hours after the onset of chest pain there is "shock" with lessening of pain and pulmonary oedema Thirdly, and rarely, some days after the infarction there is rupture of the muscular septum causing acute oedema and death, or chronic oedema with continuing orthopnoea. These three forms of attack differ from others discussed because the systemic blood pressure falls

Elderly patients suffering from ischaemic heart disease often have large hearts, sclerotic systolic murmurs, atrial fibrillation and sometimes bundle branch blocks. The height of the jugular venous pressure varies and they are often in a state of chronic pulmonary oedema. Digitalis and occasional diuretics may maintain them with only moderate disability for years. However a respiratory infection, by increasing blood volume, may cause an acute attack, but more important to appreciate is the danger of transfusion. Even small transfusions may cause disaster, and if blood is necessary because of, say, gastro-intestinal haemorrhage, it must be given slowly as packed cells, and any rise in jugular venous pressure promptly noted. If it should rise, and the patient is not already fully digitalized, digoxin can be added to the transfusion and which can be continued even more slowly Similar remarks apply to transfusing any patient with a hyperkinetic circulation. The often repeated warning of the dangers of transfusing patients with pernicious anaemia is due to fear of pulmonary oedema but, of course, such a procedure is perfectly feasible with care.

Other rare causes of acute pulmonary oedema due to left ventricular failure are ruptured aortic cusps or chordae tendinae due either to bacterial endocarditis or to operative disasters

As mentioned, pulmonary oedema following cerebral lesions appears to be due to a rise in pulmonary capillary pressure, and the clinical pattern is similar to that of left ventricular failure due to hypertension or aortic valve disease

Radiological aspects are discussed in Chapter 5. An electrocardiogram is mainly of value if it demonstrates cardiac infarction in a patient who suddenly develops acute dyspnoea. Prolongation of the arm to tongue circulation time may persist for hours or days after an attack of cardiac asthma and may help to distinguish it from respiratory asthma if other diagnostic features are equivocal.

Treatment of Acute Pulmonary Oedema

The principles of treatment are to reduce pulmonary capillary pressure, provide maximal alveolar oxygenation and decrease anxiety

The first is achieved by intravenous theophyllinethylenediamine which is not only a peripheral arterial dilator but also reduces bronchial constriction. Venesection or limb tourniquets are also effective. Ganglionic blocking agents reduce pulmonary capillary pressure as a secondary effect to reduction in systemic pressure. Why morphine, which is the classical remedy, is so effective is not known. It has been shown on many occasions not to have a primary effect on the pulmonary circulation Its action must be more subtle

and related to relief of anxiety and its effect on the respiratory centre, but neither of these explanations is satisfactory. The difficulty is in interpreting the mechanism of the action of morphine, but this does not detract from its value and it remains the drug of first importance.

Alevolar oxygenation is dependent upon the degree of bronchial obstruction due to bronchospasm and fluid within the bronchi. Oxygen therapy, by tent or mask, can improve this and is normally employed Positive pressure respiration has its advocates but it has been shown that, as the extrinsic capillary pressure rises, there is an increase in capillary pressure and the object of forced inspiration is defeated Anti-foaming agents have sometimes been used to reduce the viscosity of the high mucin and protein content. Theoretically this is sound but the practical applications have been disappointing

Relief of anxiety is normally helped by a good doctor, the sitting position, and morphine. Treatment is continued by diuretics and antibiotics for associated bronchial infections.

Prophylaxis of Pulmonary Oedema

This depends upon reduction of chronic pulmonary oedema. Digitalis is sometimes used in acute attacks in order to improve left ventricular function but the systemic pressor effect, together with the improved right ventricular output, may increase pulmonary capillary pressure and perpetuate lung oedema. Therefore, preparations such as digoxin should be given by mouth rather than intravenously and for the first two days the dosage should not be too enthusiastic.

Chronic pulmonary oedema should be treated as oedema anywhere else in the body and with diuretics, reduced salt intake and appropriate sedation Aminophyllin suppositories by their slow absorption, often contribute to more peaceful nights, which should be spent on raised pillows

Proper treatment of systemic hypertension with ganglionic blocking agents may, for years, prevent attacks of acute pulmonary oedema. In congenital or acquired aortic and mitral valve disease, surgery is bound to play an increasing part, and the advantages gained depend upon the decreasing operative mortality

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